

# 2012 consensus guidelines for the management of women with abnormal screening tests and CIN & AIS:

## Risk-based approaches

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# Disclosures

- I have no financial ties to industry

# Objectives

- At the conclusion of this session, participants should be able to:
  - Apply risk-based principles to the selection of management options for women with abnormal cervical cancer screening tests and CIN/AIS
  - Individualize management for younger women at lower risk

# Goal of screening

- The goal of cervical cancer screening is prevention of morbidity/mortality from cancer
  - Not finding CIN
  - Not finding abnormal Paps
  - Not finding HPV
- But prevention works via identification & destruction of cancer precursors

# Limits to screening

- Attempting to prevent all cancer is unrealistic and harmful
  - Cancers in youngest women may not be screen detectable
  - To approximate total prevention would require high sensitivity screen (e.g. HPV) at frequent intervals (<1y) with treatment for equivocal/mostly transient abnormalities
  - Harms outweigh benefits

# Potential harms from screening

- Stigma, disrupted relationships, anxiety/distress
- Lost time, expense of investigation for lesions destined to regress
- Pain, injury from colposcopy/treatment
- Pregnancy loss

# Screening targets

- CIN3 is precancer, though only 30-50% progress to cancer over 30y
  - But observation isn't acceptable, since which CIN3s will invade and when can't be predicted
- CIN2 is a collection of CIN3 and CIN1
  - Useful as a community threshold for treatment
  - >50% regression rate, low risk of invasion
  - observation acceptable, esp in younger women
- CIN1 is transient or stable HPV infection with minimal cancer risk: not treated

# Management follows risk

- High risk: treat by destroying TZ
- Low risk: routine screening
- Intermediate risk: manage by level of risk
  - Short interval rescreening
  - Molecular triage (HPV, genotype, p16<sup>ink4a</sup>)
  - Colposcopy with biopsy
- Definitions of high/low/intermediate risk are arbitrary, based on community balancing of risks of intervention vs risks of cancer

# Assigning intervention

- Prior guidelines based on expert assessment of risk
  - 1994: Expert panel devised interim guidelines
  - 2001, 2006: Consensus conferences
    - Incorporated ALTS RCT data, formal lit review
  - These were used to identify current risk thresholds for current guidelines
    - e.g., HPV+ ASC-US/LSIL → colpo, CIN2+ → treat

# How to think about risk

- Risk of cervical precancer or cancer condenses a battery of tests to one number
- The concept “**Similar Management of Similar Risks**” ensures simplified, consistent management of different test combinations
- 2012 guidelines build off implicit risk thresholds in prior guidelines

# 2012 guidelines are risk-based

- 2012 guidelines based on "big data"
- Risk analysis of 1.4M women from KPNC
  - >1M women age 30+ with cotesting
    - 440 cancers, 3231 CIN3+, 7581 CIN2+
  - Almost 400k women age<30 with cytology, with HPV triage for ASCUS
    - 26 cancers, 1231 CIN3+, 4193 CIN2+

# Risk analysis of KNPC data

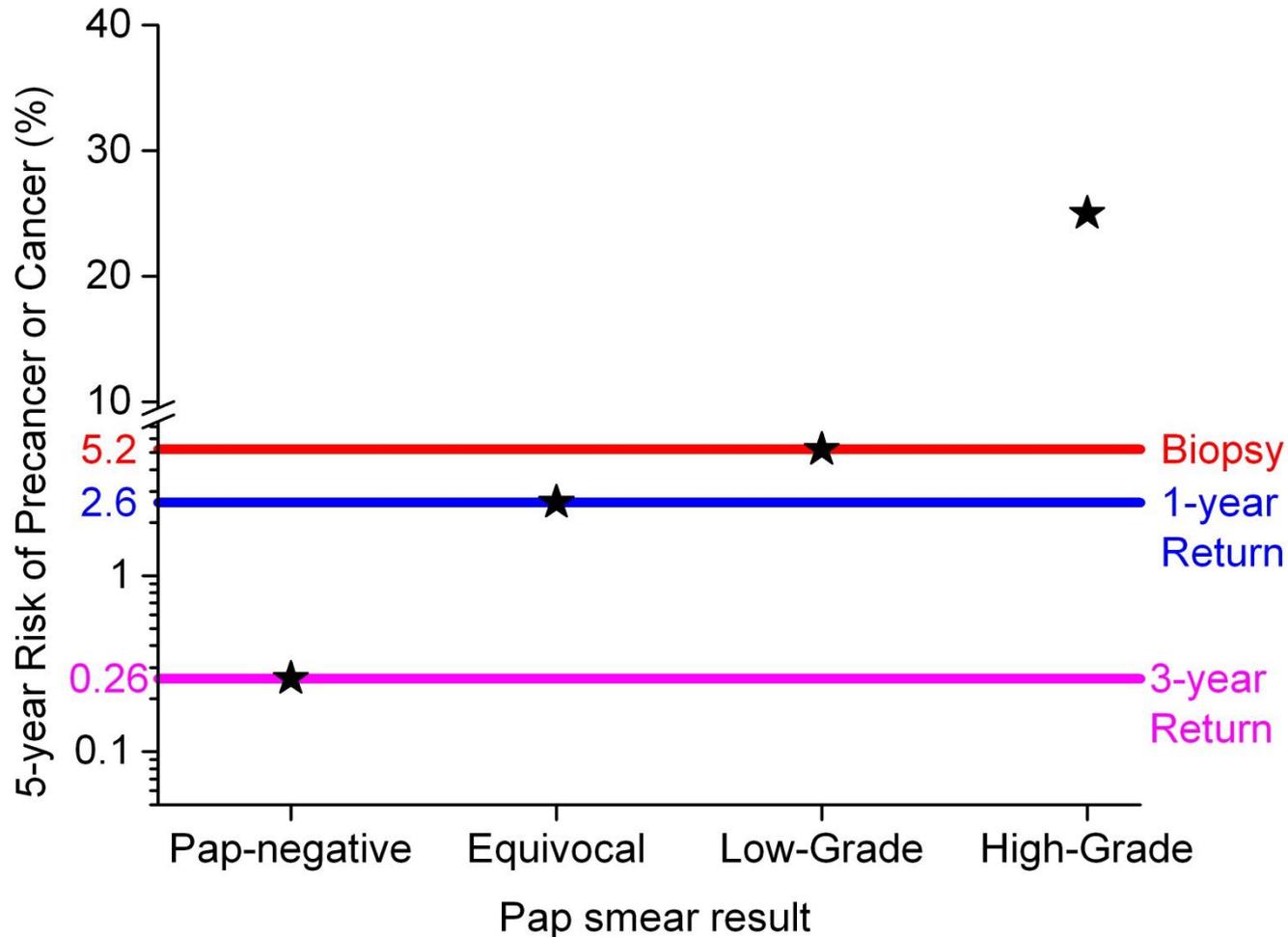
- Allows precise risk estimation for various test results & combinations
- "What are immediate and future (5y) risk after X?"
- Uses CIN2+ risk for rare events
- Assesses cancer risk when high even when CIN2,3 risk is relatively low, as after AGC Pap

# Limits to KPNC dataset

- Cannot define management of rare events
  - e.g. HPV- ASC-US x 3
- Generalizability to all US women?
- Did not obtain q6mo assessments, so utility of short-interval testing unclear
- Did not record margin status at cone/LEEP
- Database extends only 8y (2003-2010)
  - Cannot guide longer term management
  - Cannot define late attainment of risk low enough for “routine screening”

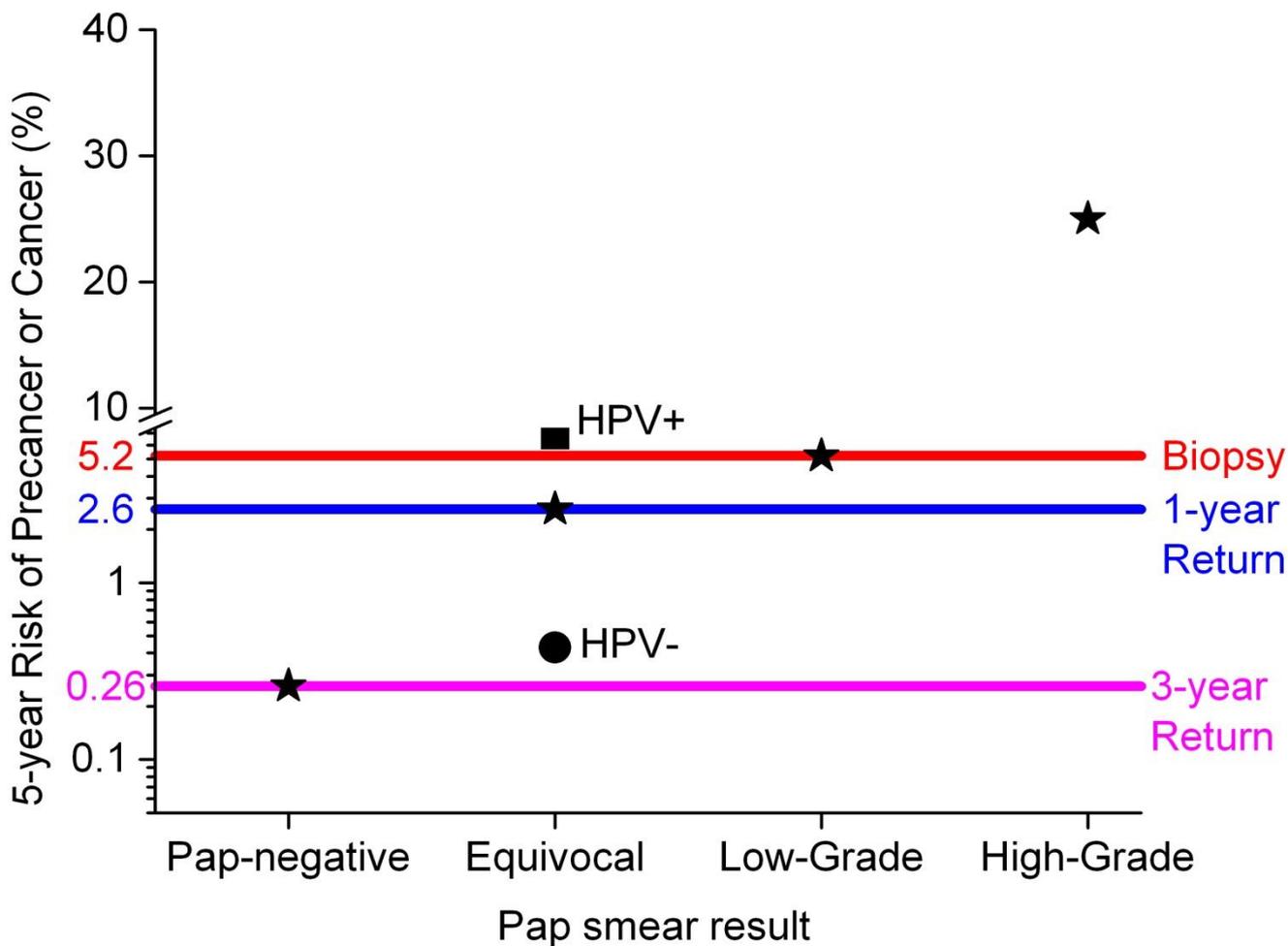
# Risk thresholds in 2006 guidelines:

Neg Pap=3y return, ASC-US=6-12mo return, LSIL=colpo



# Risk of HPV+ and HPV- ASC-US

HPV+ ASC-US has risk similar to LSIL, so similar mgmt  
HPV- ASC-US has risk close to neg Pap, so similar mgmt  
(too high for 5y return, set in 2011 screening guidelines)

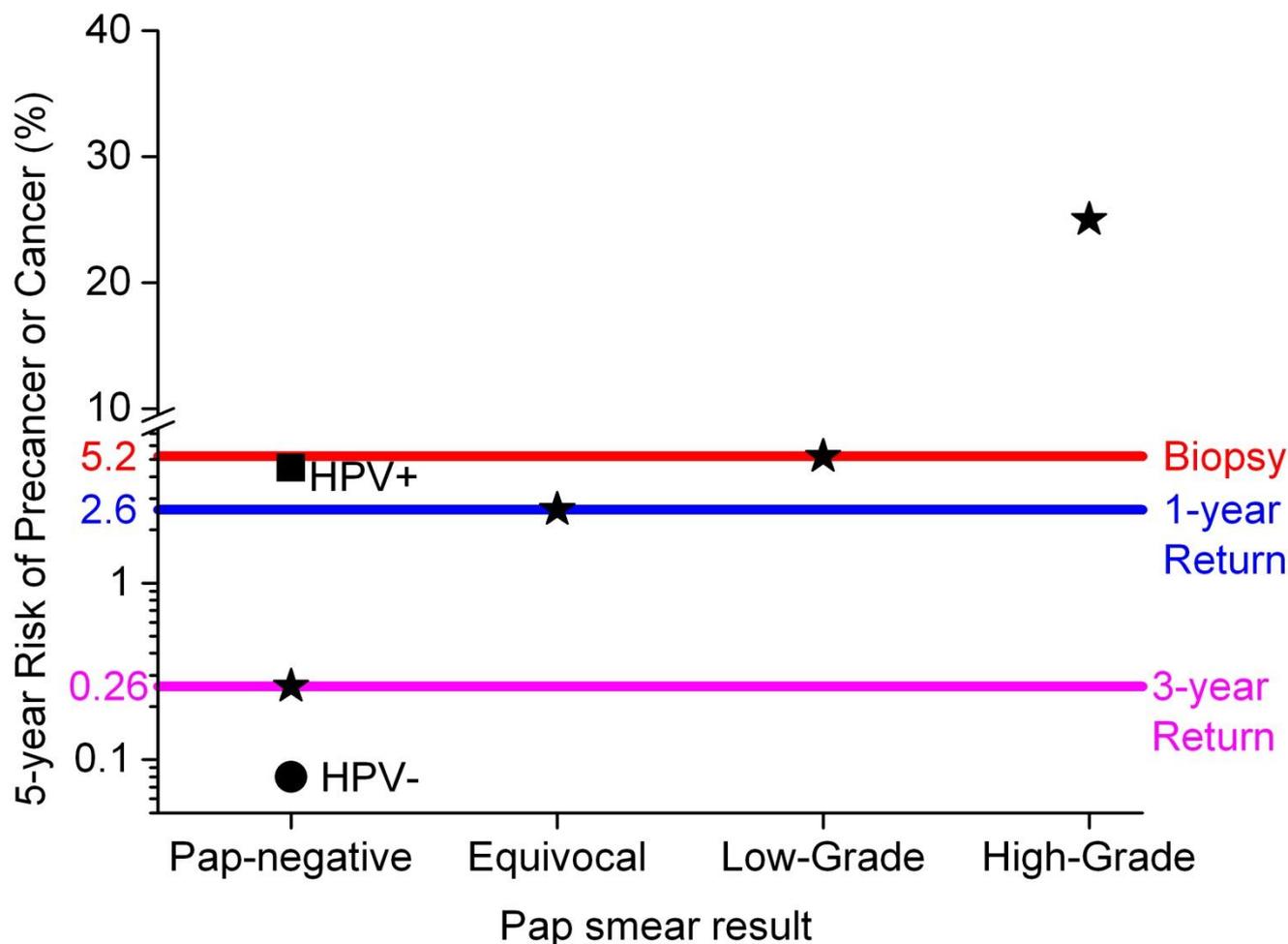


Katki et al, JLGTD  
2013;;17:S28-S35

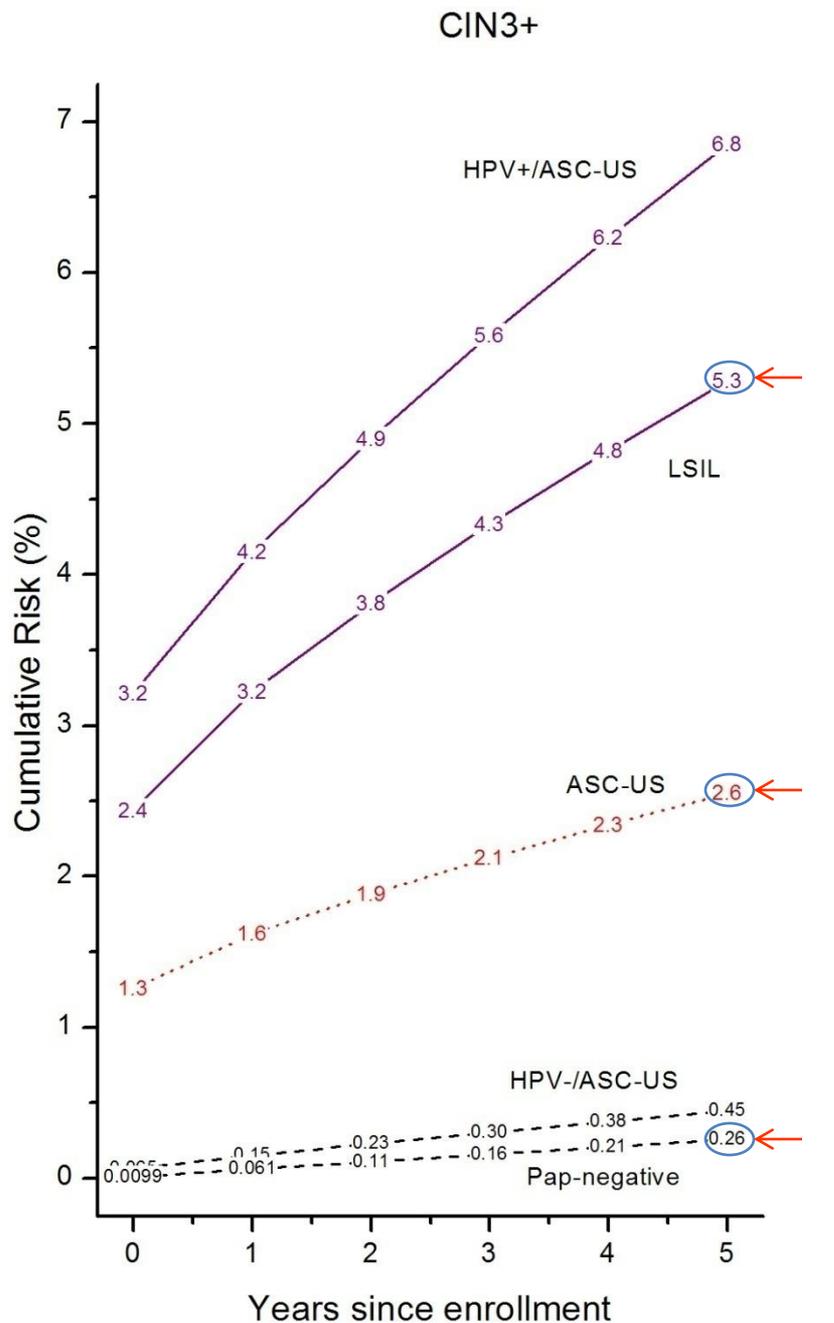
# Risk of HPV+ & HPV-/Pap- results

HPV+/Pap- risk is below threshold for biopsy (close, but colpo for all HPV+/Pap- would be an undue burden).

HPV-/Pap- women have risk  $\ll$  Pap-, so 5y return



# Another way to benchmark to implicit risk thresholds



- HPV+/ASC-US
  - Immediate risk of 3.2% > LSIL-based colpo threshold immediate risk of 2.4%
  - Thus, refer HPV+/ASC-US to colposcopy
- HPV-/ASC-US
  - 3y risk of 0.30% is very similar to the 0.16% risk threshold for Pap-negative 3y return
  - Thus refer HPV-/ASC-US for 3-year return
- Simplification: Use 5-year risk for all risk thresholds
  - For each comparison, one group is riskier than the other group at all times
  - Immediate Colposcopy: 5-year risk > 5.3%
  - 1-year return: 5-year risk ~ 2.6%
  - 3-year return: 5-year risk ~ 0.26%

**Benchmarking cotest risks to implicit 5-year CIN3+ cytology-only risk thresholds**

Current management based on cytology-only	Cytology-only 5-year CIN3+ risks (implicit risk thresholds)			Cotest 5-year CIN3+ risks		
	Cytology result	Frequency	CIN3+ risk	HPV/Cytology result	Frequency	CIN3+ risk
Immediate colposcopy (high-grade cytologies)	SCC	0.01%	83%	HPV+/ HSIL	0.20%	50%
	HSIL	0.20%	48%	HPV+/ AGC	0.05%	34%
				HPV-/ HSIL	0.01%	29%
	ASC-H	0.17%	18%	HPV+/ ASC-H	0.12%	25%
	AGC	0.21%	8.7%	HPV-/ ASC-H	0.05%	3.8%
				HPV-/ AGC	0.16%	1.1%
Immediate Colposcopy				HPV+/ ASC-US	1.1%	6.8%
	LSIL	0.92%	5.3%	HPV+/ LSIL	0.77%	6.2%
1-year return				HPV+/ Pap-	3.5%	4.5%
	ASC-US	2.7%	2.6%	HPV-/ LSIL	0.18%	2.1%
3-year return				HPV-/ ASC-US	1.8%	0.45%
	Pap-	95.8%	0.26%			
5-year return				HPV-/ Pap-	92.1%	0.08%

# Summary: Management by 5y CIN3+ Risk Thresholds

- Left side orders risks from all cytologies, banded by current management guideline
- Right side orders risks for each co-test into the risk band
- Managing cotest results by these benchmarked implicit risk thresholds ensures “Similar management of similar risks”

# Additional impetus for 2012 guidelines

- 2011 ACS/ASCCP screening guidelines changed expectations
  - Managing discordant cotests?
  - How often is “routine screening”?
  - Managing adolescents/young women?
- New data on Paps read as unsat/absent EC/TZ component
  - Prior guidelines never validated in conf
- Data on outcomes after CIN1 on ECC
- New technology added options
  - HPV genotyping

# Consensus development process

- ASCCP created 6 working groups
  - Addressed issues defined by ASCCP
  - Led by ASCCP Practice Committee co-chairs and national experts.
  - Working groups staffed by delegates from >20 professional societies, federal agencies, US/ international cancer prevention organizations
  - Met in Bethesda MD, Sept 14-15, 2013
  - All recommendations accepted by >2/3 vote

# Disclaimer

- These guidelines are based on best available evidence
  - High quality evidence not available for all questions
  - Some guidelines based solely on expert opinion
- Guidelines should never substitute for clinical judgment
  - Guidelines cannot apply to all clinical situations
  - Judgment should be used in applying guidelines to individual clinical situations

# Caution on HPV testing

- Recommendations on use of HPV testing are based on controlled trials using validated HPV assays
  - Clinicians can't assume similar results when management is based on results of assays not similarly validated.
    - Patient harm may result
  - Labs must use only HPV tests validated to ensure reproducibility and accuracy in identifying cancer precursors, as documented by FDA approval or peer reviewed publication
  - No role for LRHPV testing

# Why not HPV testing alone?

- Currently available HPV tests lack mechanism for assessment of squamous cellularity
  - Neg test may be falsely neg if insufficient cells
- Concurrent Pap test controls for cellularity
- Cotesting more familiar
  - HPV testing not approved as a stand-alone test

# Treatment and pregnancy

- **Women with LEEP were more likely to have**
  - **Preterm birth (O.R. 1.7)**
    - **LBW (O.R. 1.8)**
    - **PPROM (O.R. 2.7)**
- **Single studies show association with perinatal death, incompetent cervix**
- **Similar findings after cold knife, laser cone**

# Terminology

- **Recommended:** Good data to support use when only one option is available
- **Preferred:** Option is the best (or one of the best) when there are multiple other options
  - **Acceptable:** One of multiple options when there is either data indicating that another approach is superior or when there is no data to favor any single option
- **Not recommended:** **Weak evidence against an option that carries minimal risk** (*This was new in 2012*)
  - **Unacceptable:** Good data against use

Adapted from Wright et al JAMA (2002;287:2120-2129)

# Changes from 2006 guidelines: I

- Cytology negative/lacking endocervical cells can be managed without early repeat.
- CIN 1 on endocervical curettage should be managed as CIN 1, not as +ECC.
- Unsatisfactory cytology requires repeat even if HPV negative.
- Genotyping triages HPV+/16-18+ women to colposcopy only after negative cytology
  - Colpo indicated for all women with HPV+ ASC-US, regardless of genotyping result.

# Changes from 2006 guidelines: II

- For ASC-US cytology, immediate colposcopy is not an option.
  - Serial cytology option for ASC-US incorporates cytology at 12 months, (not 6 & 12months)
  - Then if negative, cytology every 3 years.
- HPV- ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results insufficient to allow exit from screening at age 65 years.

# Changes from 2006 guidelines: III

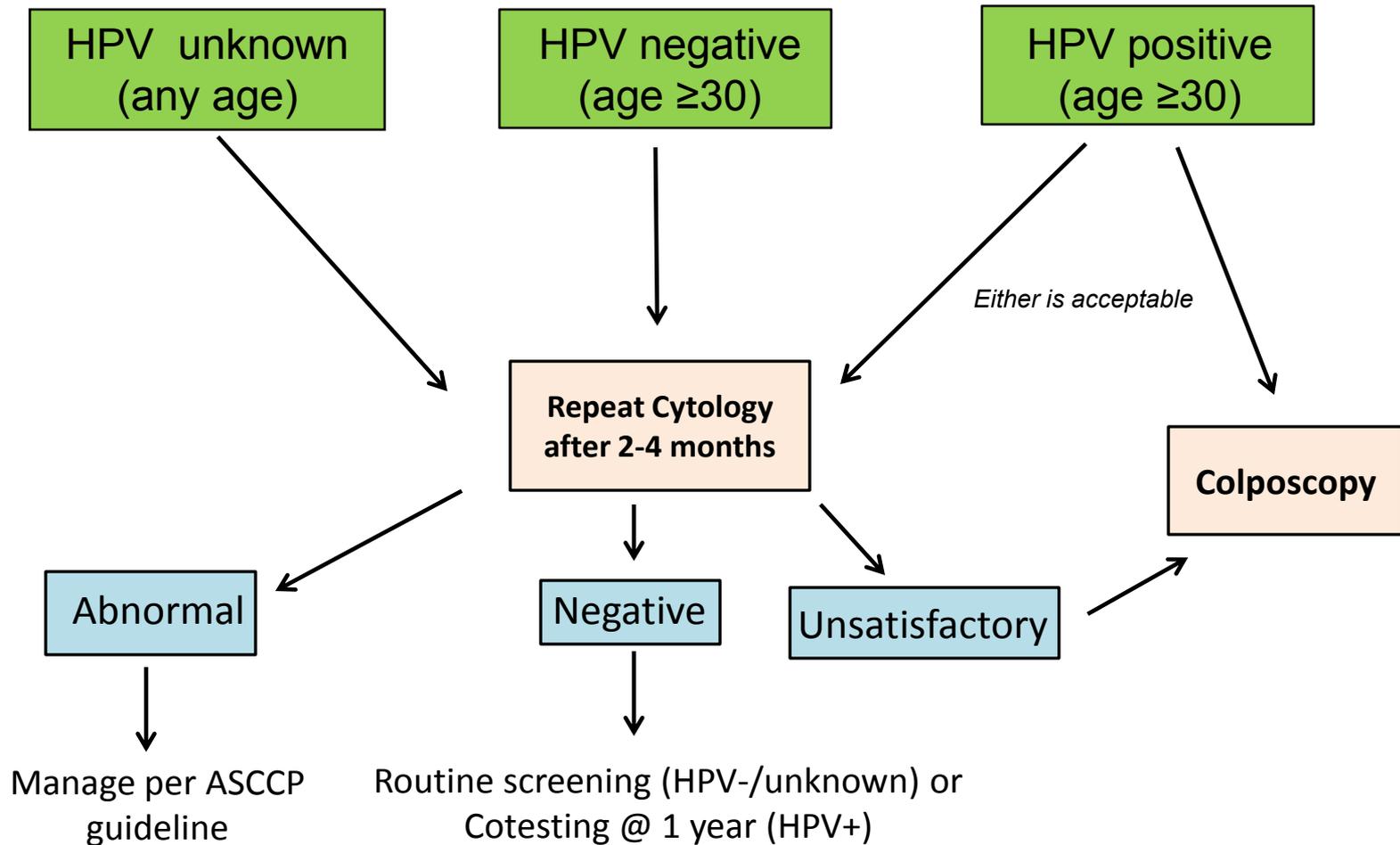
- The pathway to long-term follow-up of treated and untreated CIN 2+ is more clearly defined by incorporating co-testing.
- More strategies incorporate co-testing to reduce follow-up visits.
  - Pap-only strategies now limited to women <30yo, but co-testing is expanded even to women younger than <30yo in some circumstances.
- Women aged 21-24 years are managed conservatively.

# 2012 ASCCP guidelines

# Unsatisfactory cytology

- Accounts for <1% of all Paps
- With liquid-based cytology, usually results from hypocellularity
- Some HPV tests lack squamous cellularity control, so neg result is unreliable with unsat
- CIN3+ risk after HPV+/unsat cytology is unclear

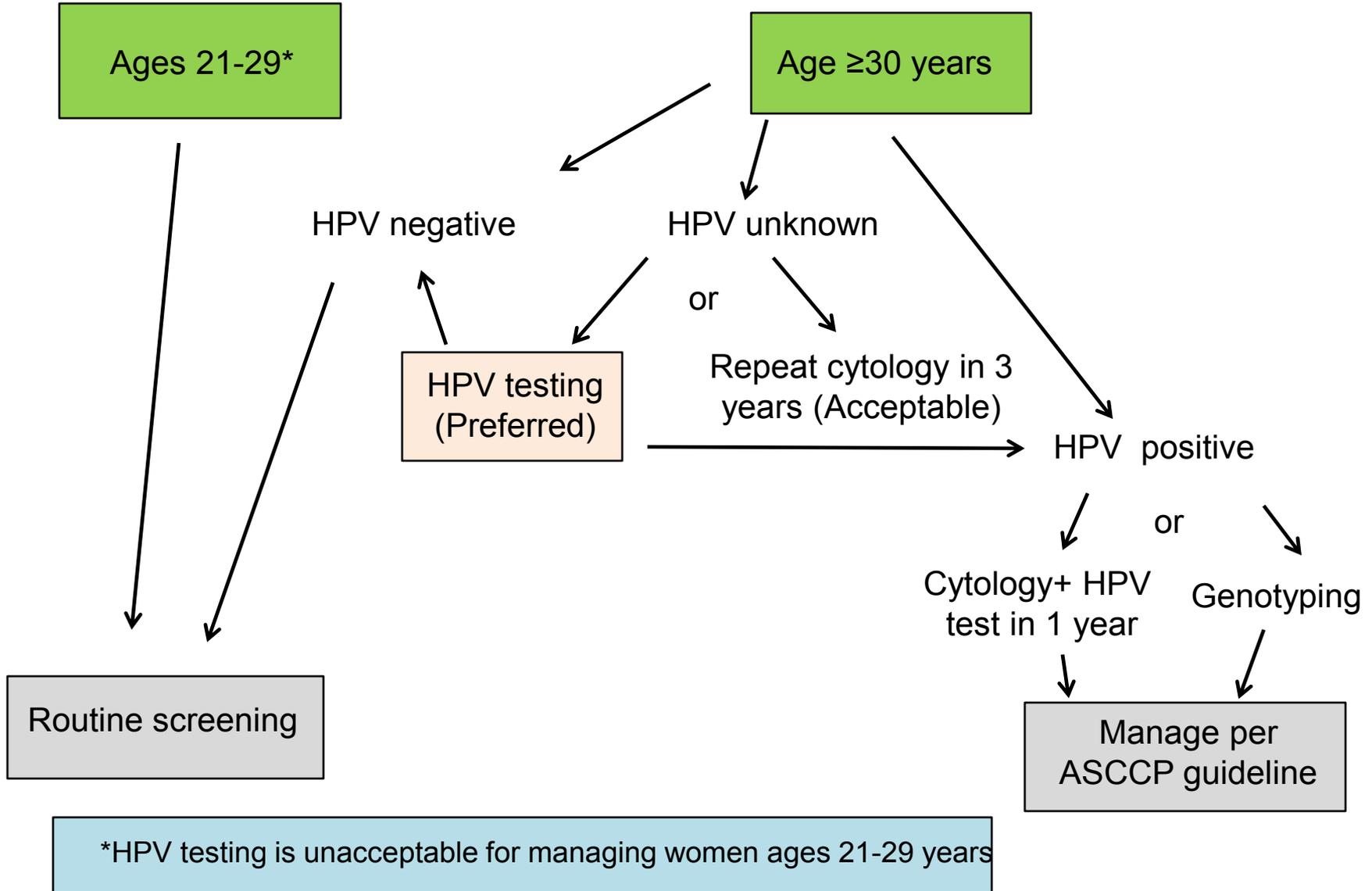
## Unsatisfactory Cytology



# Pap neg but no EC/TZ component

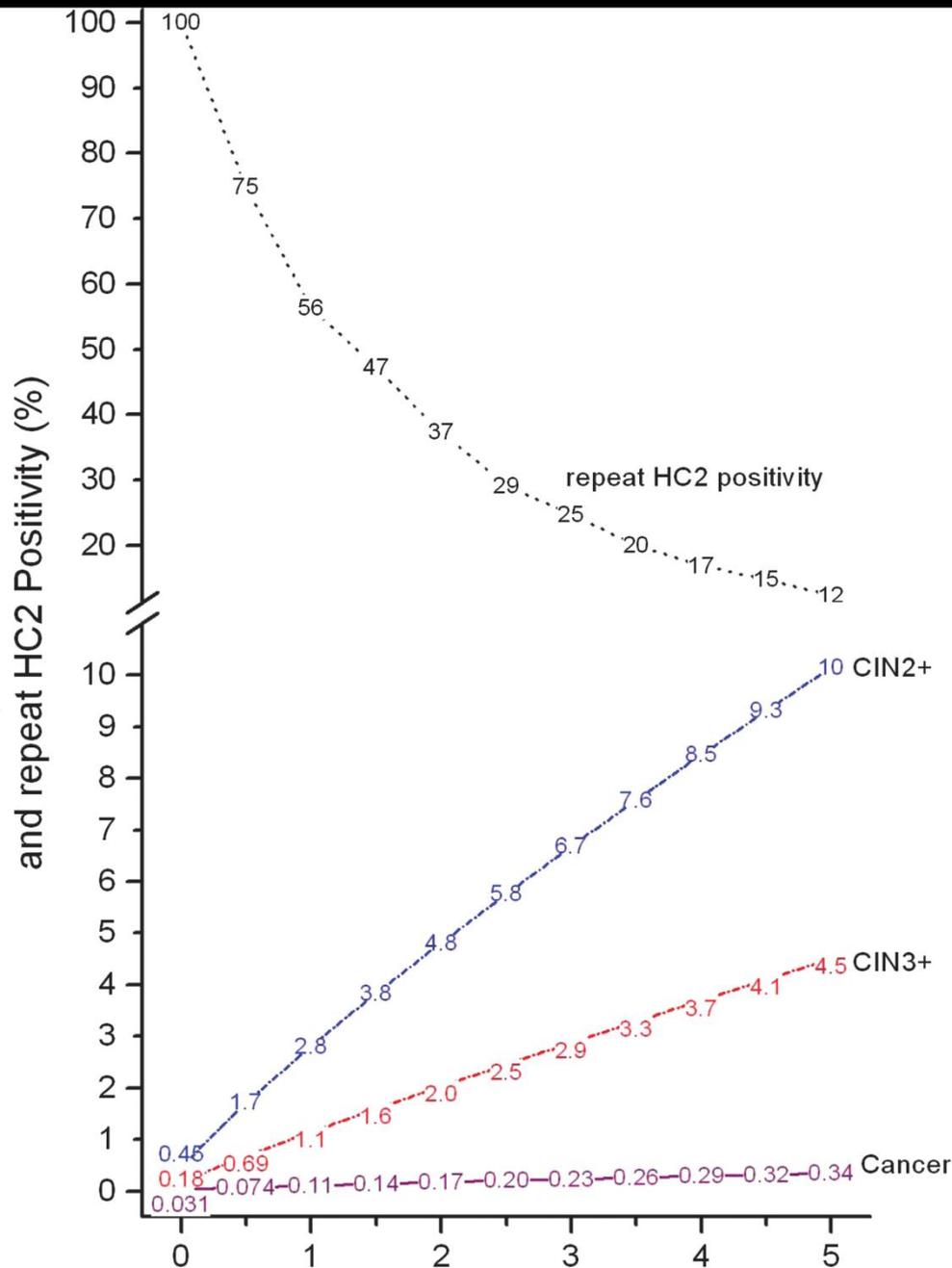
- Occurs in up to 10-20% of Paps
- Missing endocervical/metaplastic cells
- Since most cancers arise near SCJ, not clear if all areas at risk were sampled.
- But risk for CIN3+ is NOT greater in follow-up, indicating lesions not missed.
- HPV results independent of TZ sampling
  - Neg result has good NPV

# Cytology NILM but EC/TZ Absent/Insufficient



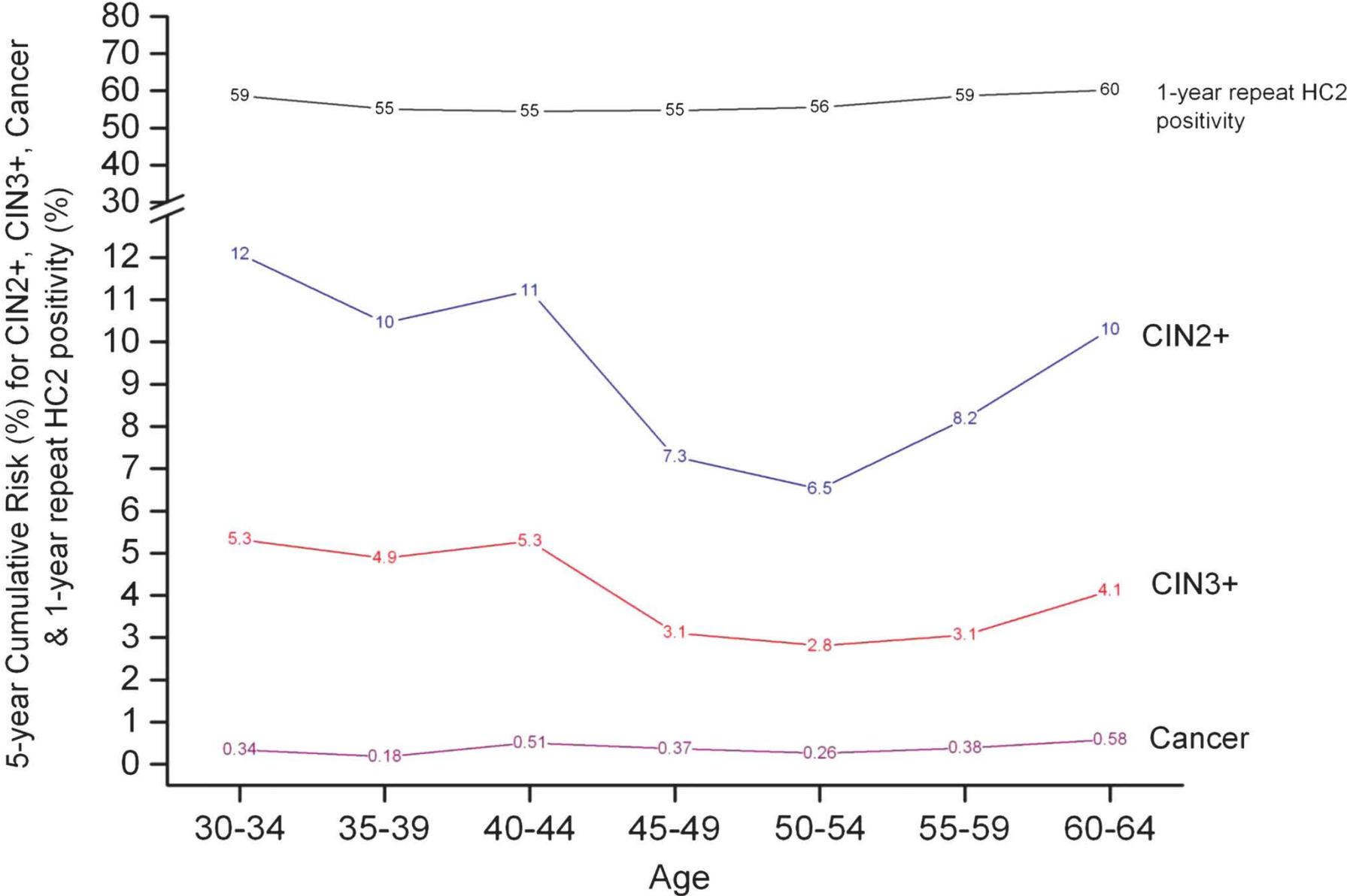
# Cytology negative, HPV positive

- Occurs in 5-10% of cotests among women 30-64
- CIN3+ risk is higher than after Pap-/HPV- result
- But CIN3+ risk insufficient to justify colpo for all
- Risk is increased if HPV positivity persists
- Women with HPV 16/18 are at particularly high risk of CIN3+ despite neg Pap ( $\approx 10\%$ )
  - HPV18 linked to adenocarcinoma, sometimes missed by Pap alone



Clearance of HPV  
and risk of disease  
across time among  
women ages 30-64  
who were  
HPV+/Pap- at  
baseline

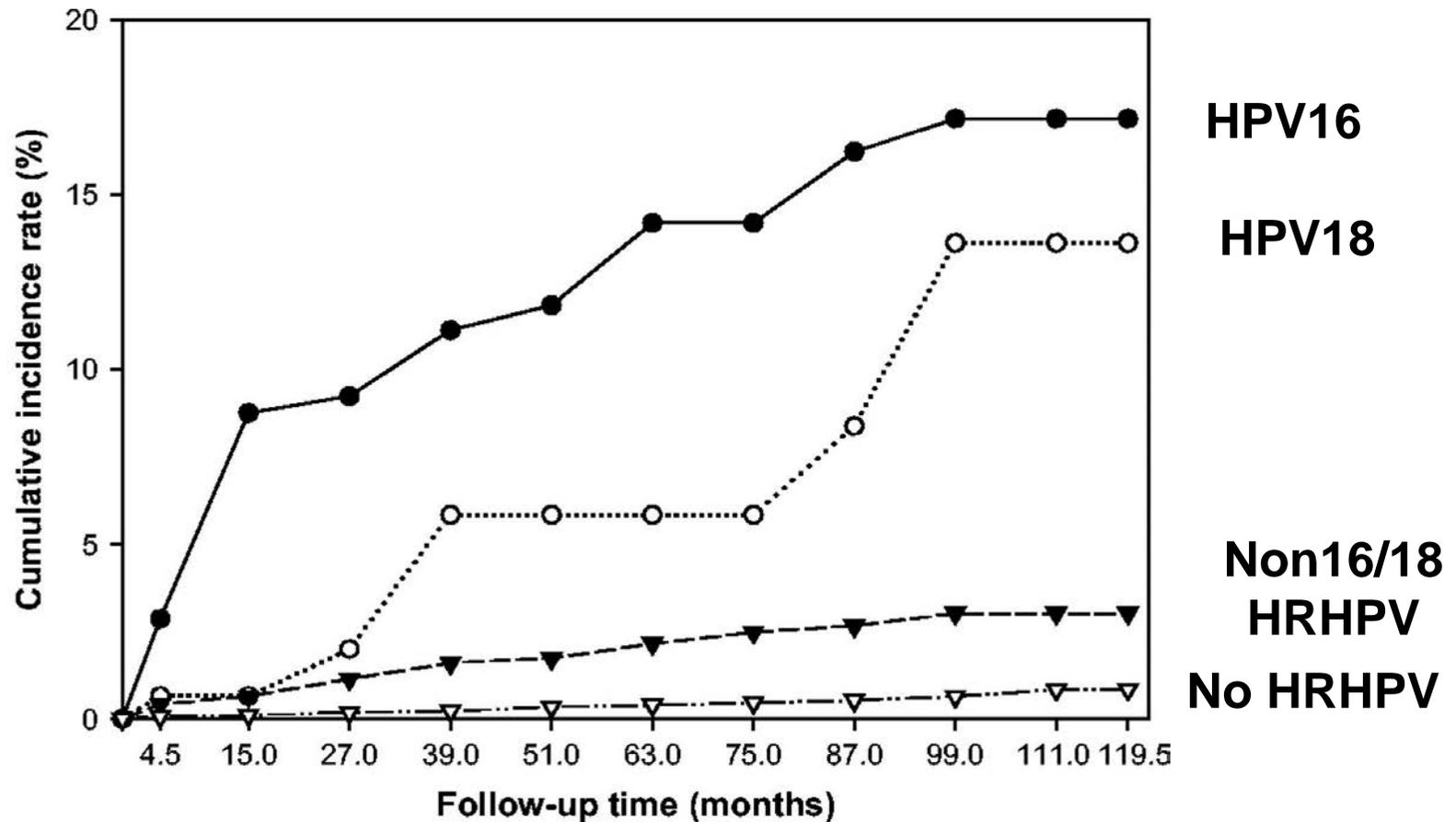
# 5y risks among women 30-64 after HPV+/Pap- result



# HPV genotyping

- Both DNA and mRNA tests available
  - Prognostic information seems similar
- HPV 16 carries 5y risk of CIN2+ of >10%
- HPV 18 risk is lower, but HPV 18 is associated with high cancer risk, esp adenocarcinoma
- ASCCP guideline does not recommend for or against genotyping: allows clinician discretion

# Cumulative incidence of CIN3+

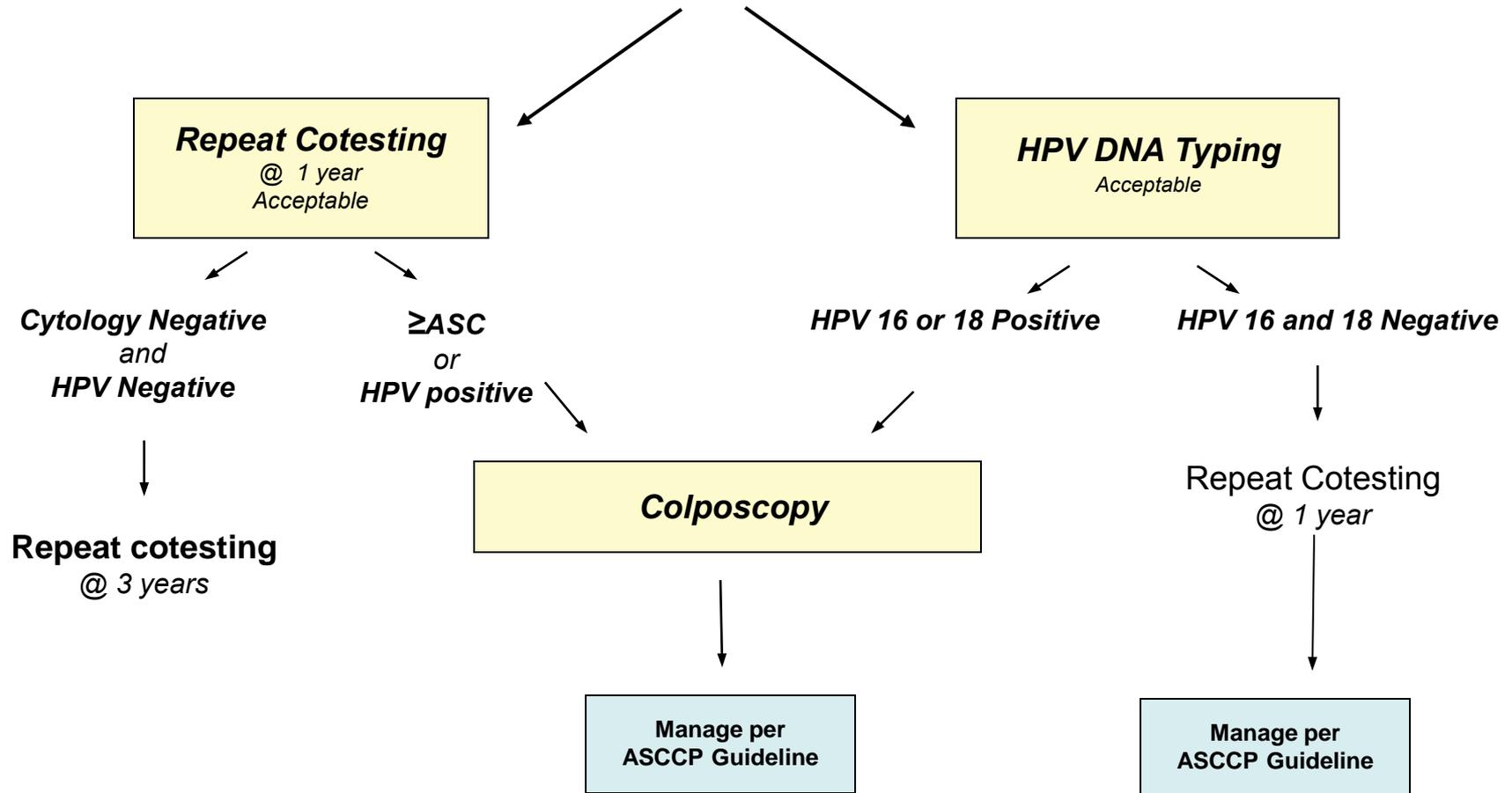


No. of women seen during follow-up interval

HPV16+	455	247	190	144	125	112	94	84	89	35	3
HPV18+	154	85	74	51	43	41	36	37	35	16	1
HC2+	2211	1208	1016	862	755	701	600	528	547	256	17
HC2-	17391	9759	8672	7813	7136	6479	5960	5551	5278	2621	156

Khan M J et al. JNCI J Natl Cancer Inst 2005;97:1072-1079

# Management of Women $\geq$ Age 30, who are Cytology Negative, but HPV Positive



# Managing ASC-US

- Reported in about 5% of all Pap tests
- 33-66% are HPV-associated
  - HPV testing about 95% sensitive for CIN2+
  - Specificity roughly doubled to >60%
  - HPV+ more often in younger women (>60% if <25yo but <25% if 45-55yo), those with more partners
  - HPV triage of ASC-US more cost-effective than repeat cytology

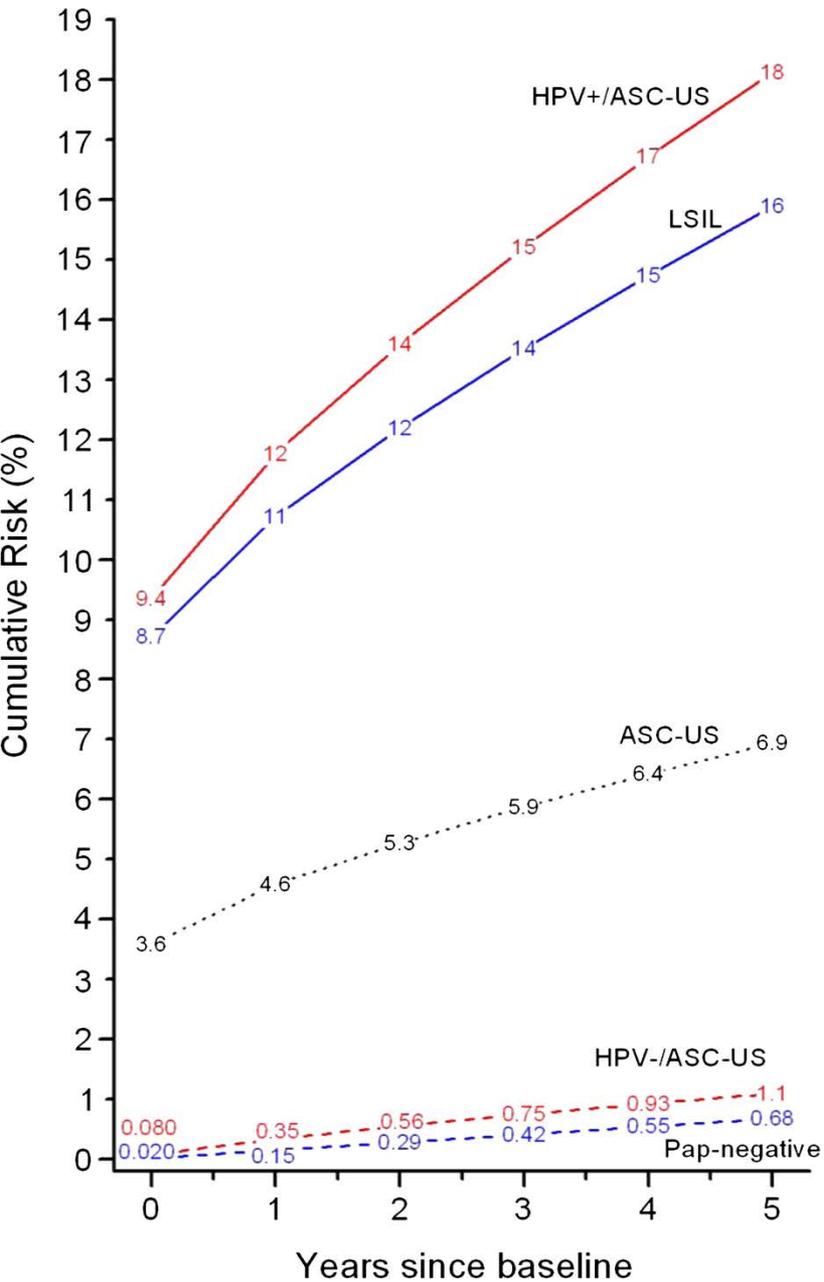
Arbyn M et al Vaccine 2006;24:S3:78-70

Eltoum IA et al Cancer 2005;105:194-99

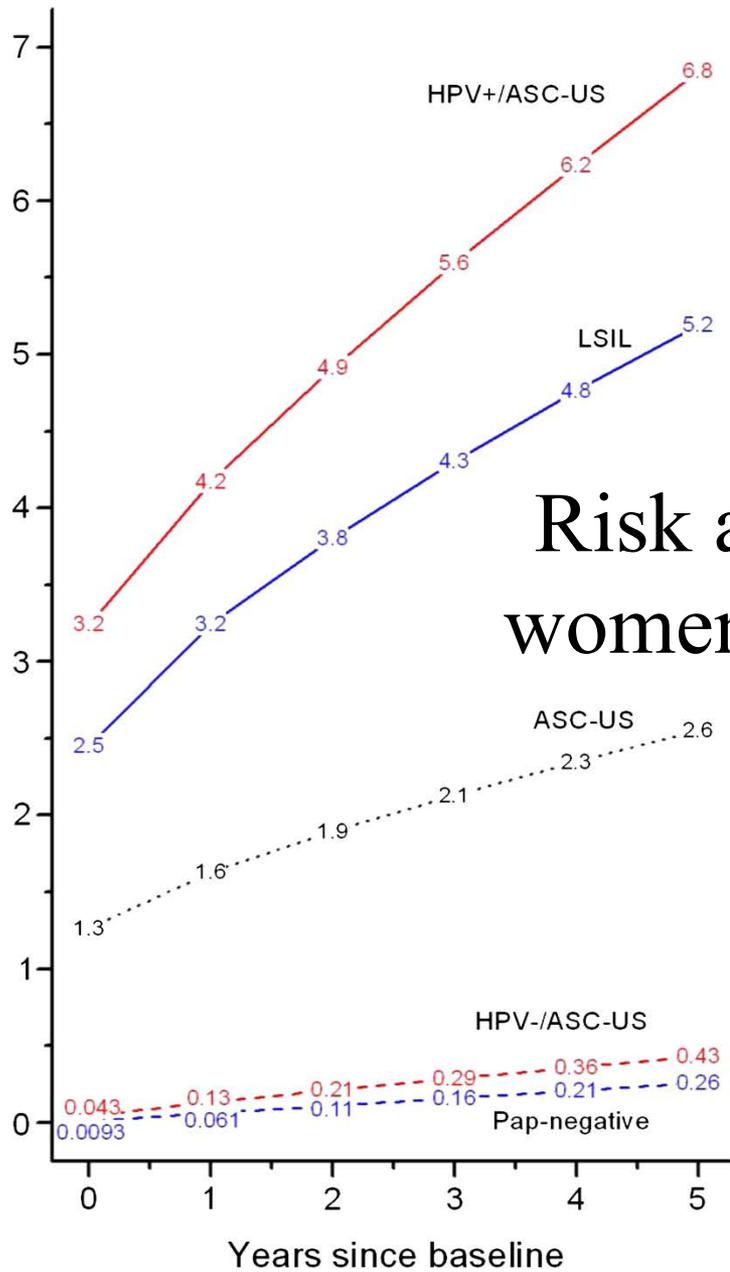
# Managing ASC-US

- Reported in about 5% of all Pap tests
- 33-66% are HPV-associated
  - HPV testing about 95% sensitive for CIN2+
  - HPV+ more often in younger women with more partners
- Removal of ASC-H from ASCUS in 2001 Bethesda revision decreased CIN3+ risk
  - CIN3+ risk after ASC-US in KPNC < risk in ALTS
- For women >60yo, cancer risk after HPV- ASC-US > after HPV-/Pap-
  - Requires retesting in <5y (contrast 2011 screening recs)
- CIN3+ risk for HPV+, 16/18- ASC-US requires colpo

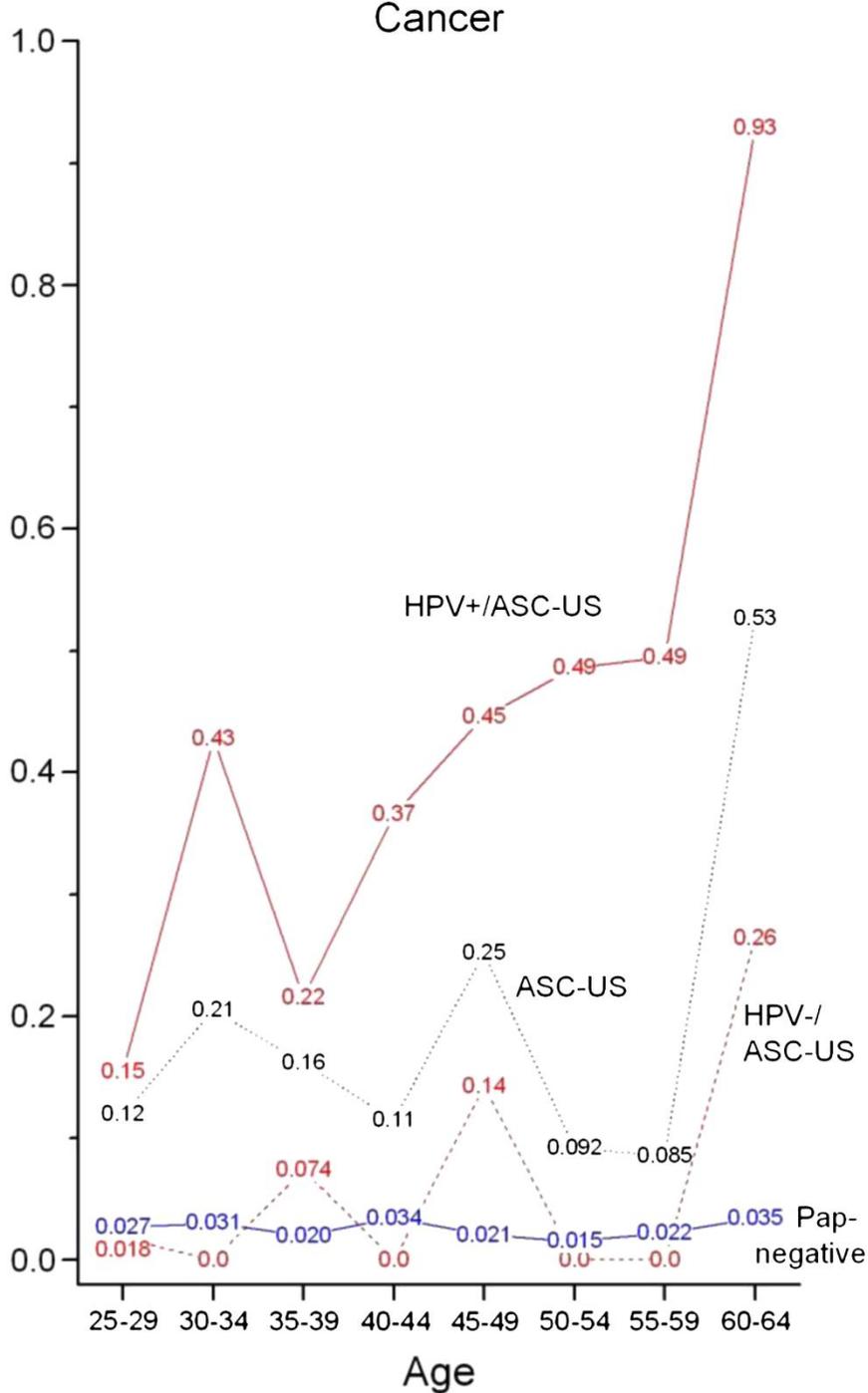
CIN2+



CIN3+



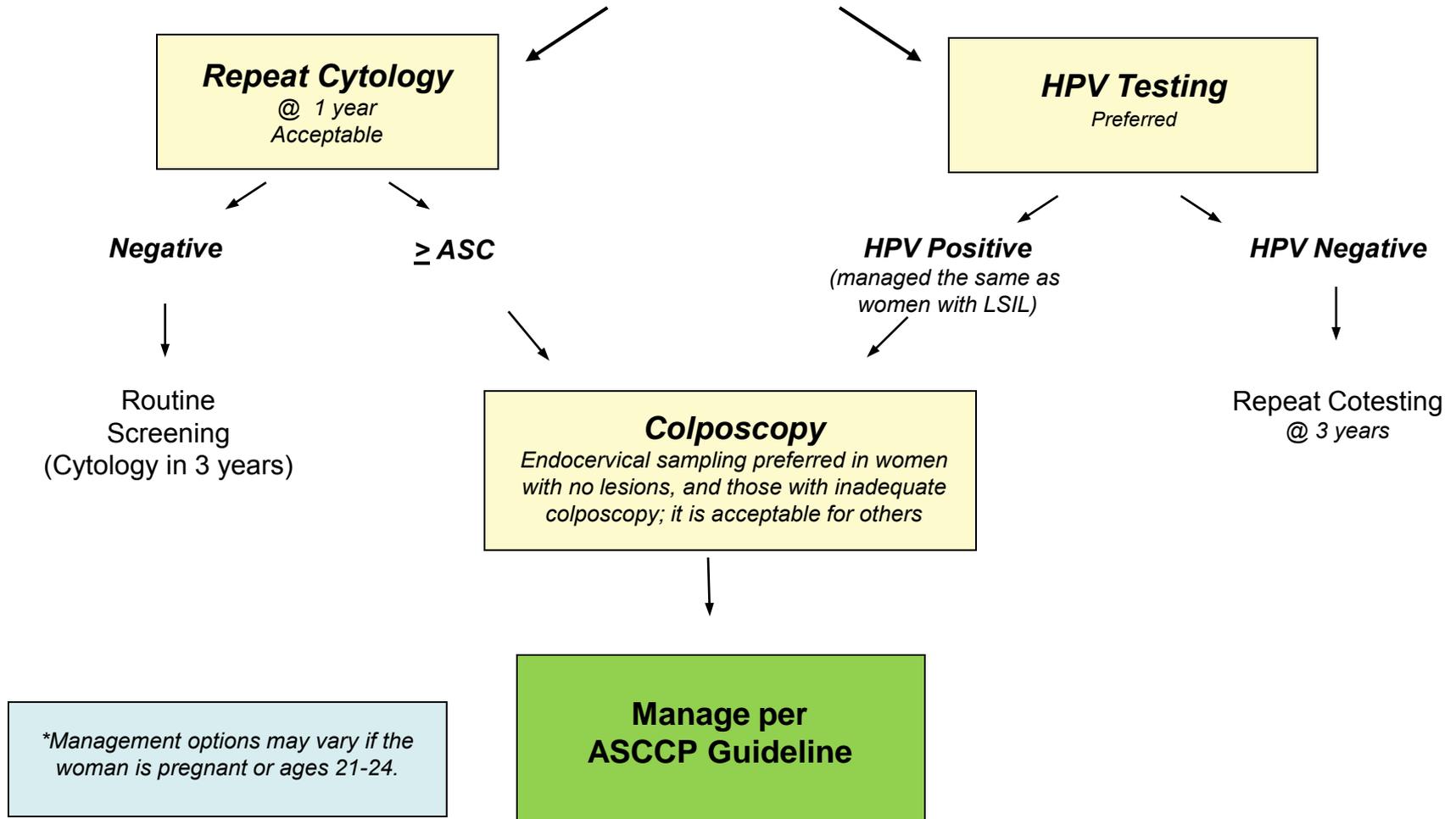
Risk among women 30-64



Cancer risk after ASC-US  
vs neg cytology among  
women 30-64:

Note higher risk among  
60-64yo women. This  
was confirmed in women  
>65yo, leading to  
recommendation to  
continue screening after  
HPV- ASC-US—not  
considered neg to allow  
exist from screening

# Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology\*



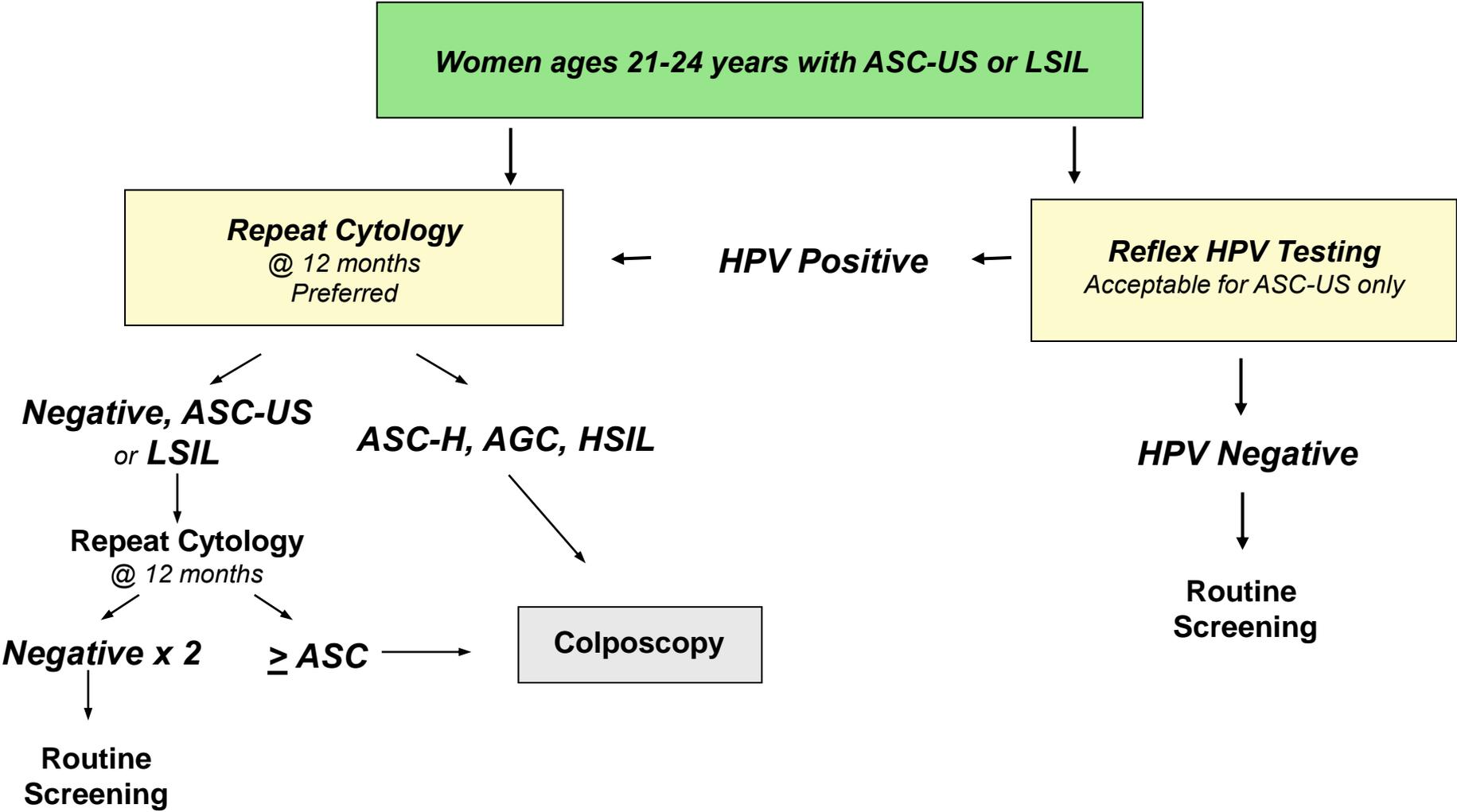
# Managing women 21-24

- Risk of cancer remains low (about 2/million)
- In KPNC dataset, only 3 cancers in 133,947 women 21-24yo
  - One cancer in 11,280 with ASC-US (HPV+)
  - No cancers in 4,810 with LSIL
- HPV risk is peaking
- Likelihood of future conception is high
- Most CIN2 that is found will regress

# LSIL among women ages 21-24

- 5y CIN3+ risk only 3% after ASC-US & LSIL
- 5y CIN3+ risk only 4% after HPV+ ASC-US
  - Both significantly lower than for older women
- 5y CIN3+ only 0.6% after HPV- ASC-US
  - Compare risk of 0.2% after neg Pap
  - Low risk when HPV+/- means HPV triage alters management minimally: not required

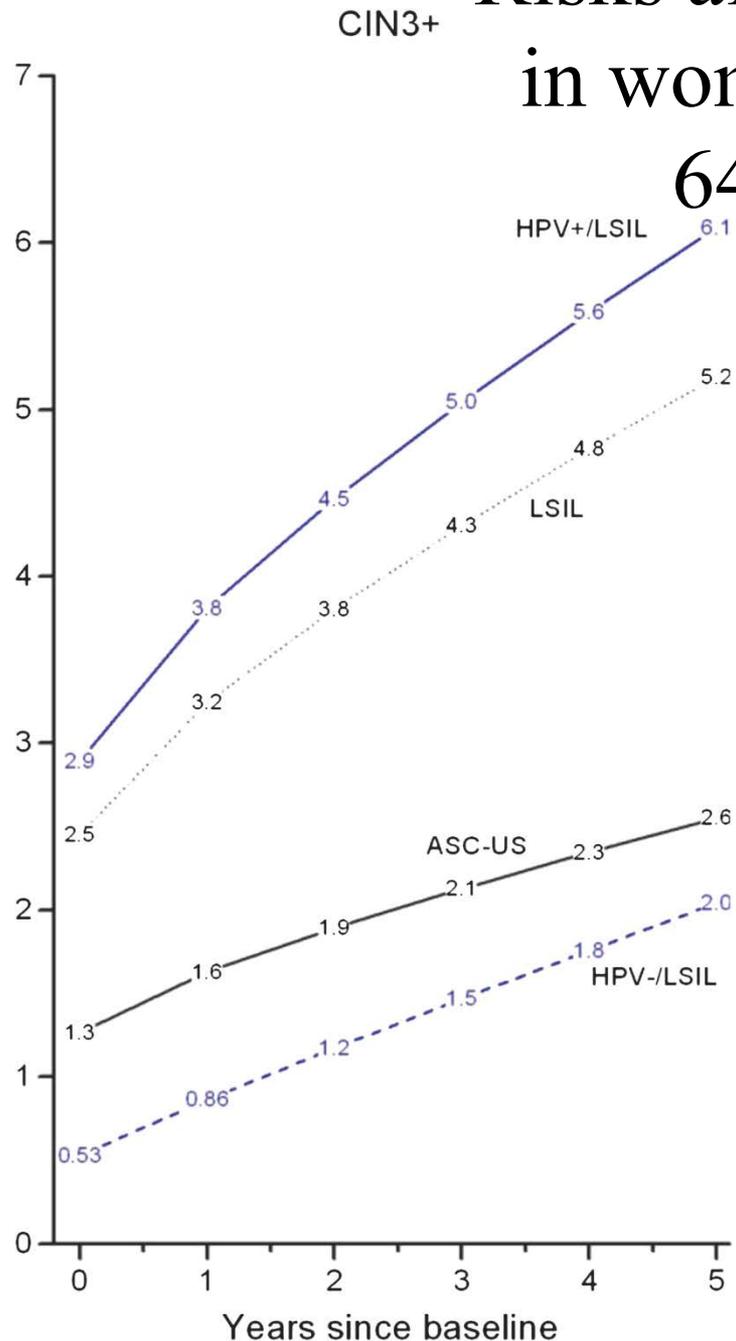
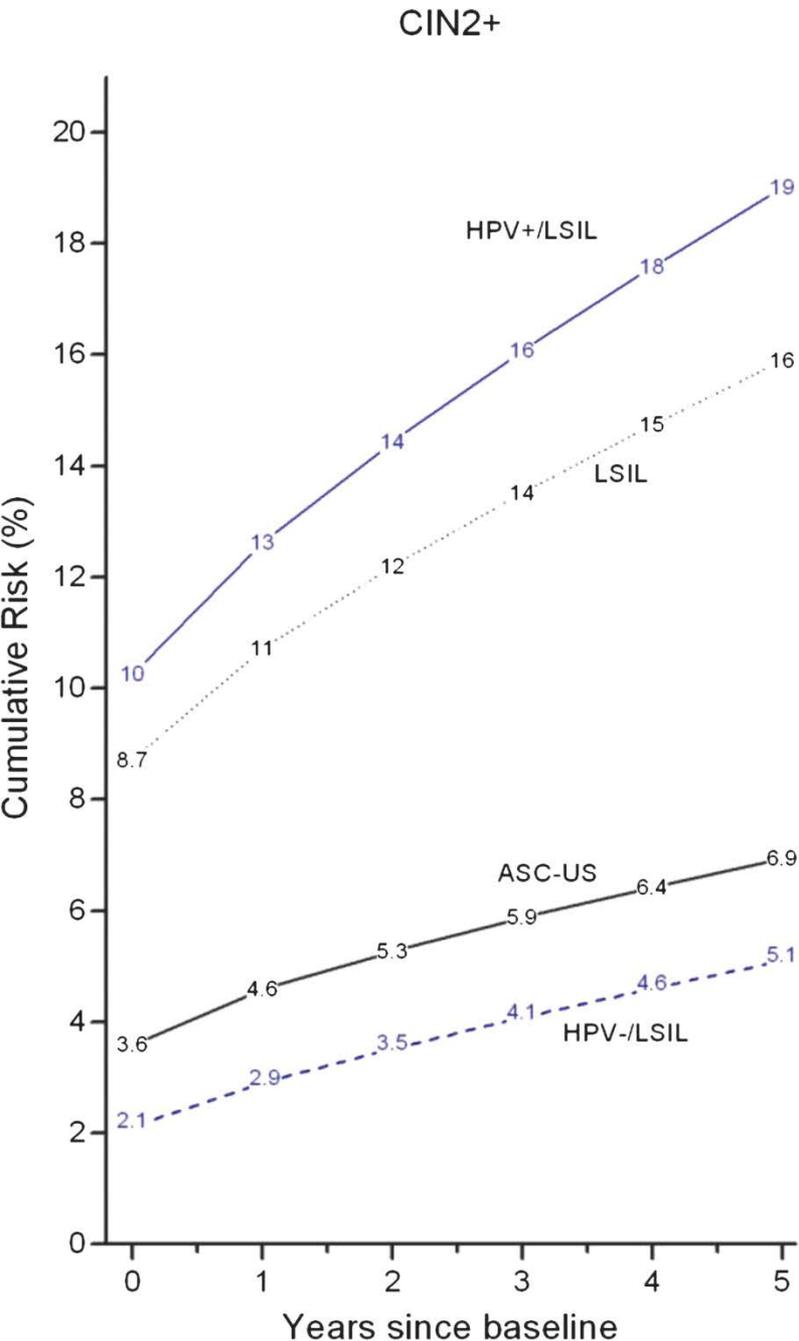
**Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)**



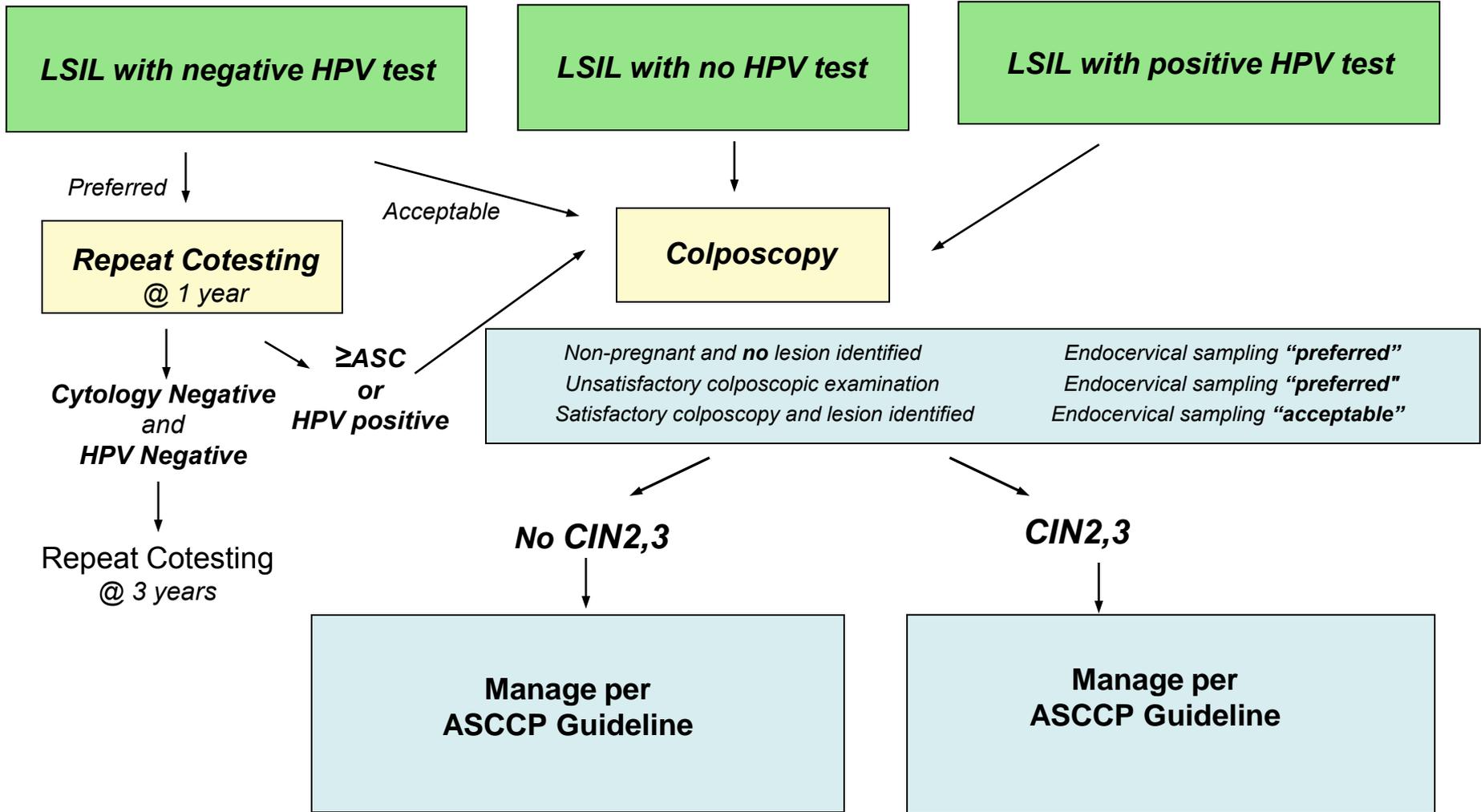
# Managing LSIL

- 2-3% of cytology specimens
- LSIL and HPV+ ASC-US have similar CIN3+ risks and clearance rates
- About 75% are HPV+
  - Too many for efficient HPV triage
- However, when HPV- LSIL obtained in women 30-64 at cotesting, 5y CIN3+ risk is only 2%
- 67% have CIN1/HPV effect at colposcopy
- Risk of cancer is <0.5% after LSIL

# Risks after LSIL in women 30- 64yo



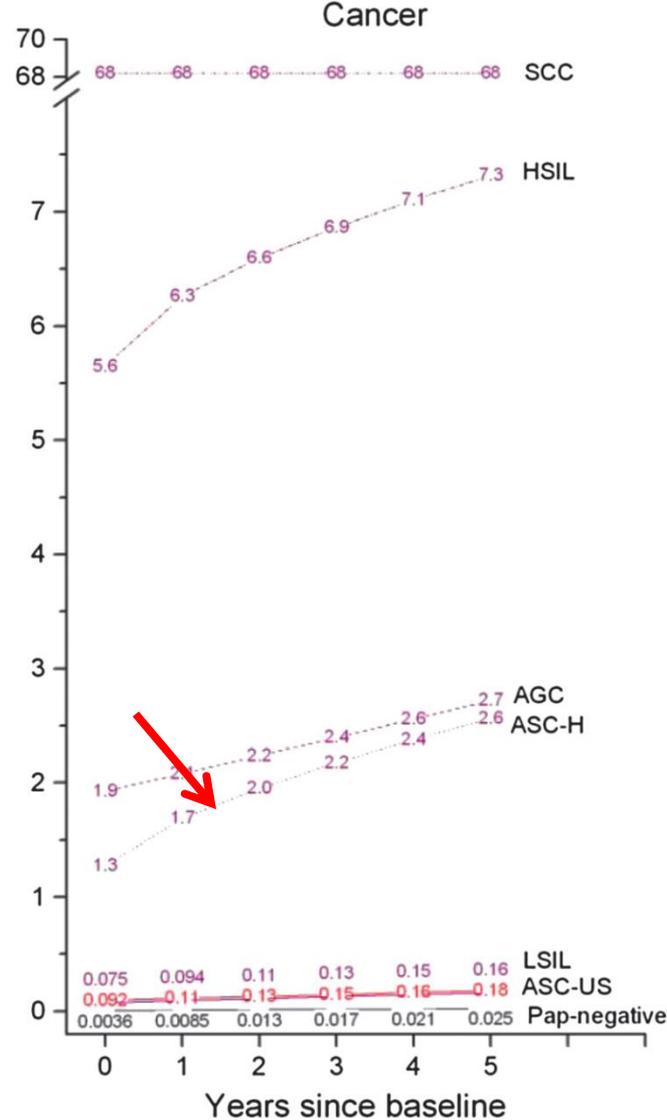
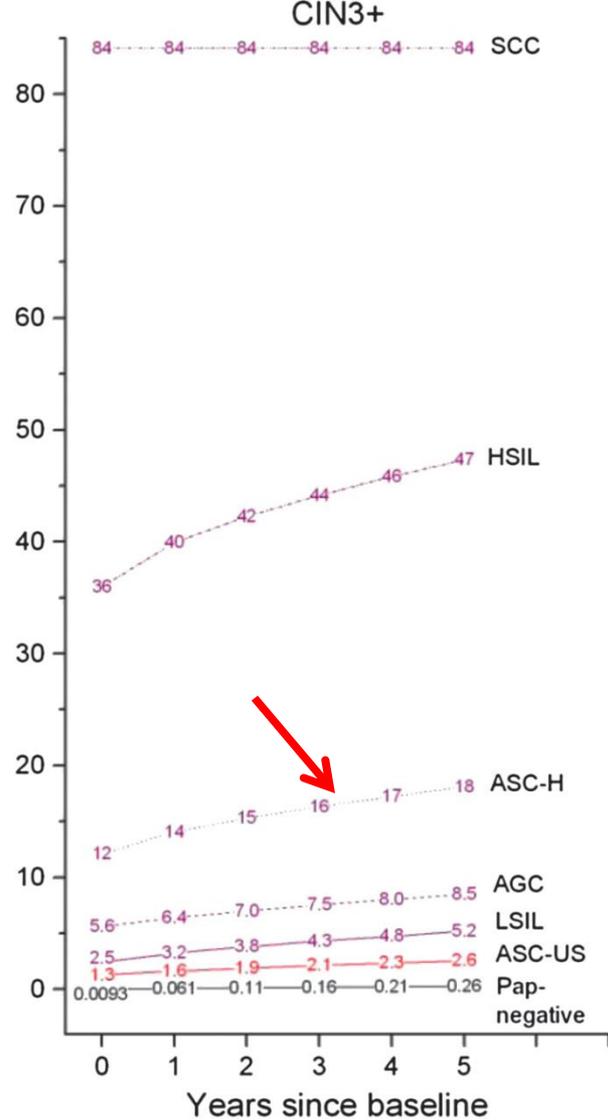
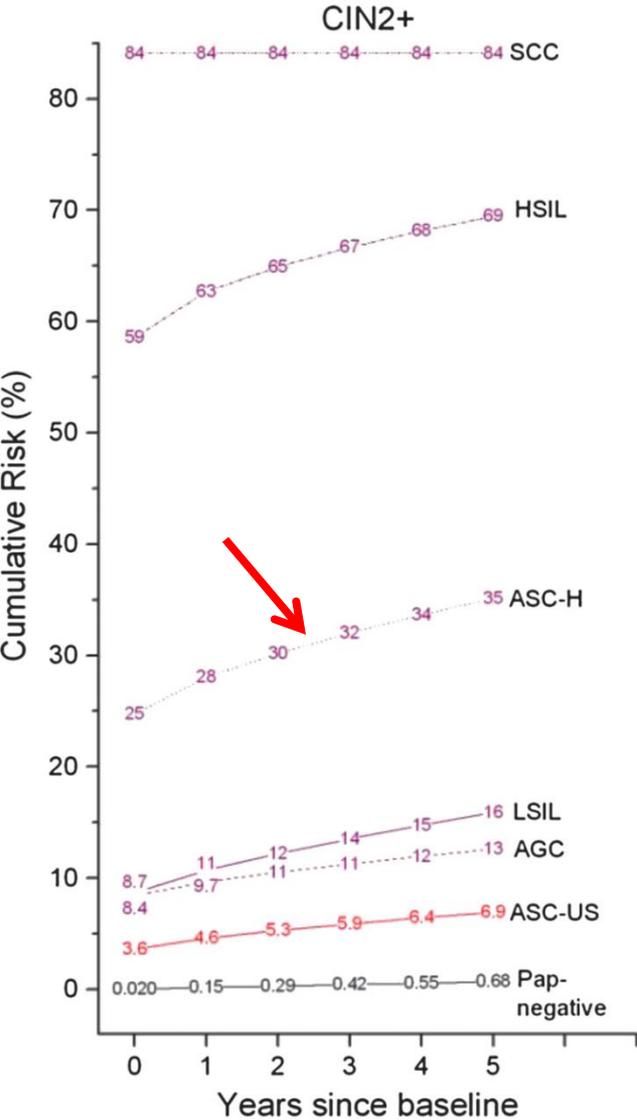
# Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)\*



\* Management options may vary if the woman is pregnant or ages 21-24 years.

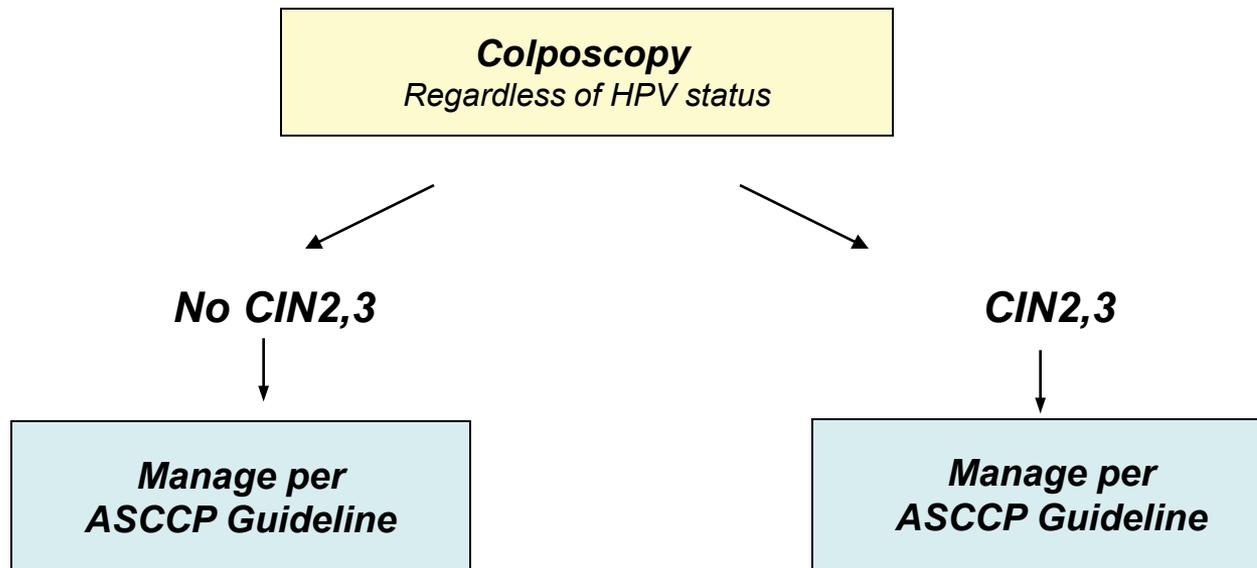
# Managing ASC-H

- Found in 0.5% of cytology specimens
- CIN3+ risk at 5y = 18% among women 30-64
- >60% are HPV+
  - HPV triage relatively inefficient
  - CIN3+ risk when HPV- = 3.5% at 5y
  - CIN3+ risk when HPV+ = 25% at 5y



Risk after ASC-H is intermediate between ASC-US/LSIL & HSIL

# Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)\*



\* Management options may vary if the woman is pregnant or ages 21-24 years.

# ASC-H, HSIL, AGC in women 21-24yo

- Risk is higher than after ASC-US/LSIL
- 5y CIN3+ risk in KPNC dataset among 21-24yo:
  - 28% after HSIL
  - 16% after ASC-H
  - 7% after AGC
- But 5y cancer risk among 21-24yo only 0/0/1%
  - Cancer is unlikely during extended observation

# Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

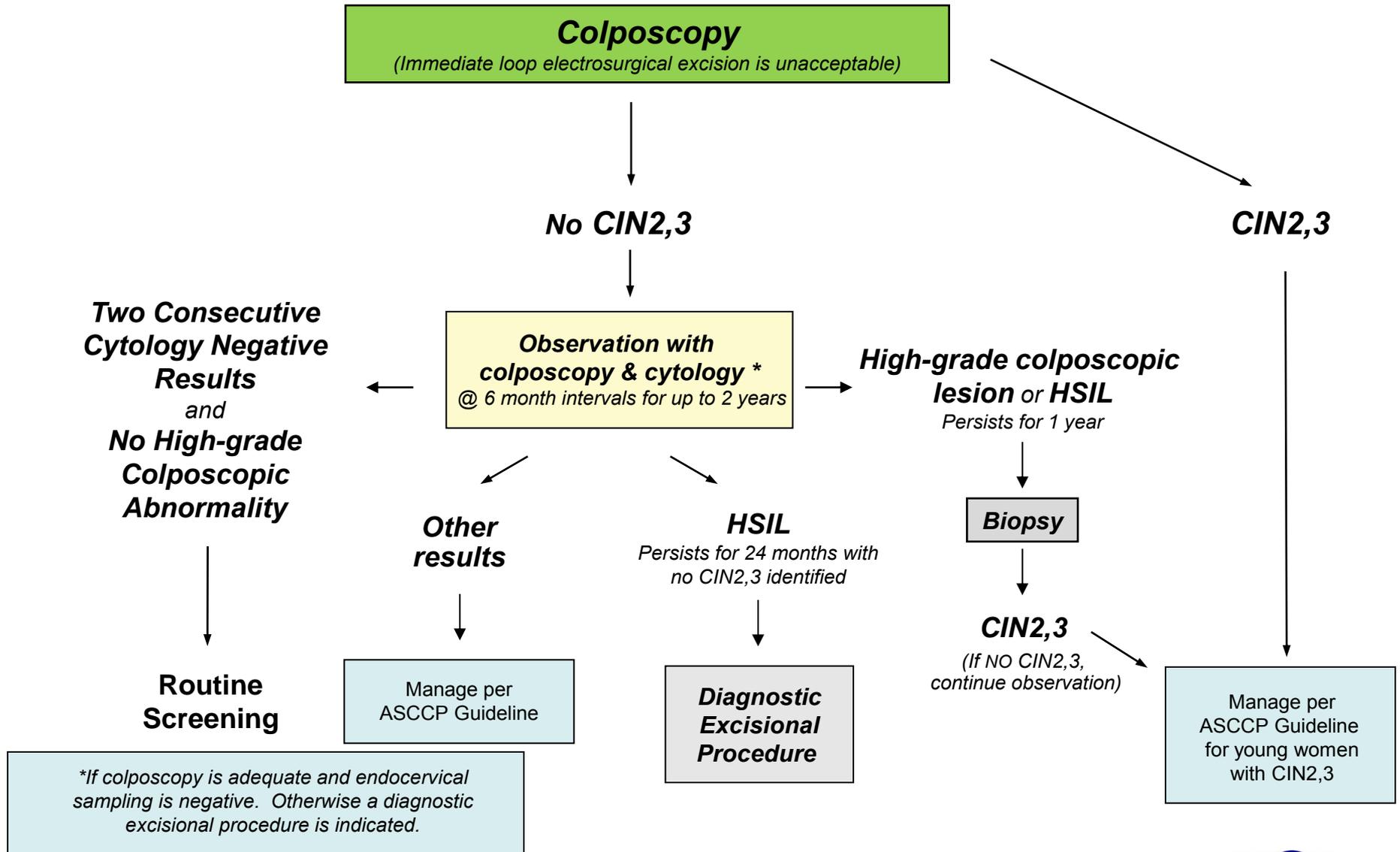


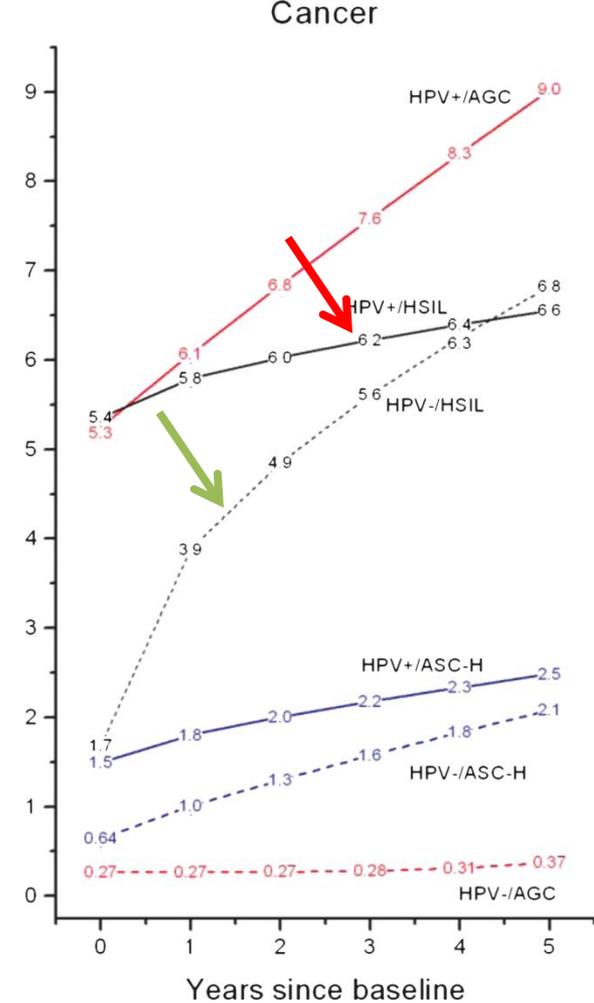
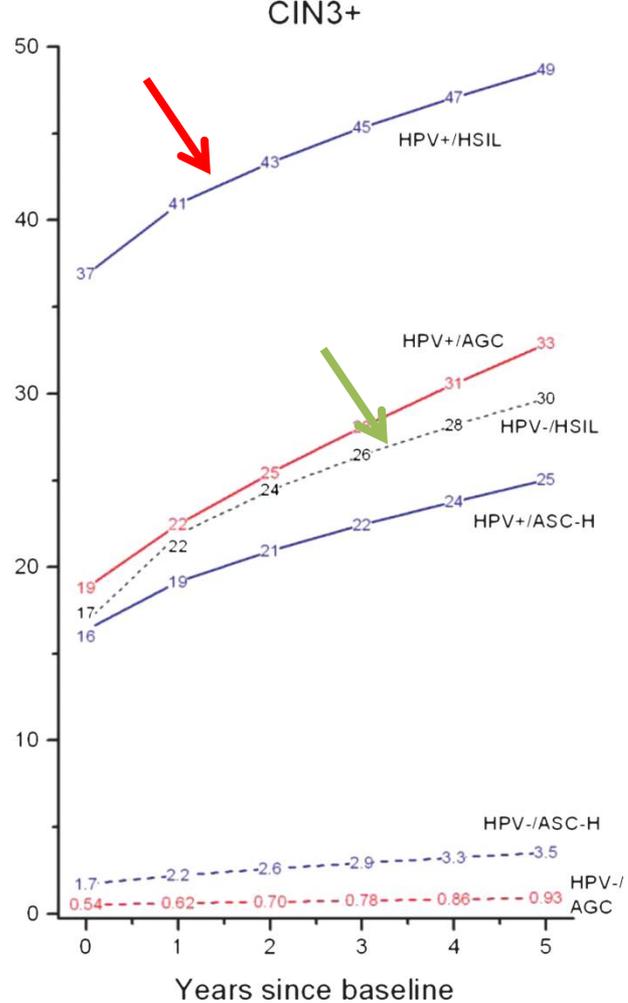
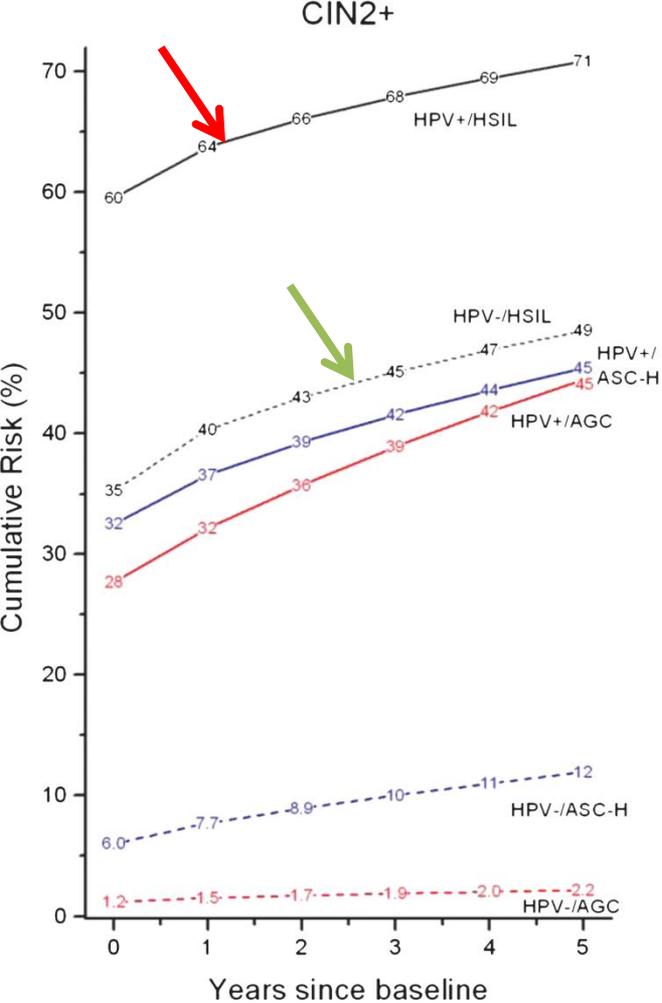
Fig. 9

# Management of HSIL

- HSIL is reported in about 0.5% of Pap tests
  - Peak incidence in women 20-29yo
- About 90% are HPV+: no role for HPV triage
- CIN3+ risk is 36%, rising to 47% at 5y
  - Justifies immediate excision when pregnancy not at issue
- 6% of women 30-64 with HSIL have cancer

# Management of HSIL in cotesting

- When HPV results are known after cotesting
  - 35% of women 30-64 with HPV- HSIL have CIN2+
    - Risk rises to 49% at 5y, when 7% have cancer
  - HPV+ HSIL has immediate CIN2+ risk of 60%, with cancer in 5%
    - Risk rises to 71% at 5y, when 7% have cancer



HPV+ HSIL has very high immediate risk for CIN2+:

→ Consider see-and-treat

HPV- HSIL has lower immediate precancer risk but

50% 5y precancer and similar 5y cancer risk

→ Still needs close obs or treatment

# Recommendations for Managing Women with HSIL: Rationale for immediate excision

- Prevalence of CIN2,3 is high
  - Most will require excision later
- Requiring extra visits for colposcopy impairs compliance and raises costs
- The sensitivity of colposcopy is suboptimal
  - In ALTS, only 54% of CIN3 found at intake colpo

Adapted from Numnum et al , J Lower Genital Tract Dis 2005;9:2-6 & Shafi et al, Br J Obstet Gynaecol 1997;104:590-4 and ALTS Group. Am J Obstet Gynecol 2003;188:1383-92.

# Recommendations for Managing Women with HSIL: Rationale against immediate excision

- Prevalence of CIN1 or no lesion is significant
  - Especially true in younger women
- Some CIN2 lesions will resolve
  - Especially true in younger women
- Once colpo excludes cancer, progression to cancer is uncommon in short term
  - Especially true in younger women

Adapted from Ostor. Int J Gynecol Pathol 1993;12:186-92.

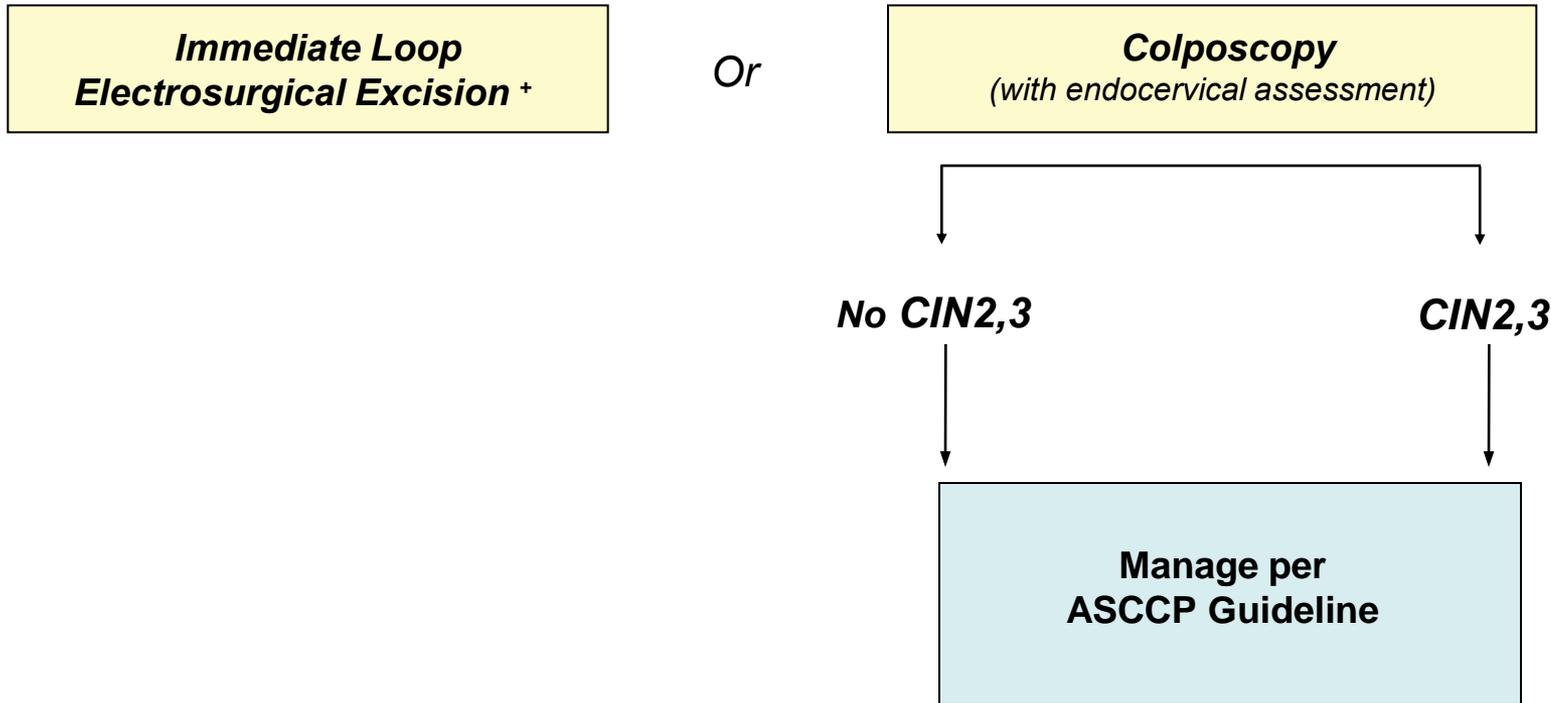
# HSIL in Special Circumstances:

## *Pregnancy*

- Colposcopy in pregnancy is complicated by vascular and epithelial changes that accentuate normal and abnormal findings.
- Biopsy may result in discomfort, cost, bleeding
  - Multiple biopsies cannot be done
- Failure to do biopsy associated with missed cancers postpartum
- Risk of cancer postpartum is <10%, and most recent studies suggest risk has fallen with time.
- Many oncologists follow pregnant women with Stage I cancer to viability
  - Missed microinvasive focus may not be clinically significant.

Cristoforoni et al. J Lower Genital Tract Dis 1999;3:225-30. Roberts et al. ibid,1998;2:67-70. Boardman et al. J Reprod Med 2005;50:13-18.

# Management of Women with High-grade Squamous Intraepithelial Lesions (HSIL)\*



\* Management options may vary if the woman is pregnant or ages 21-24

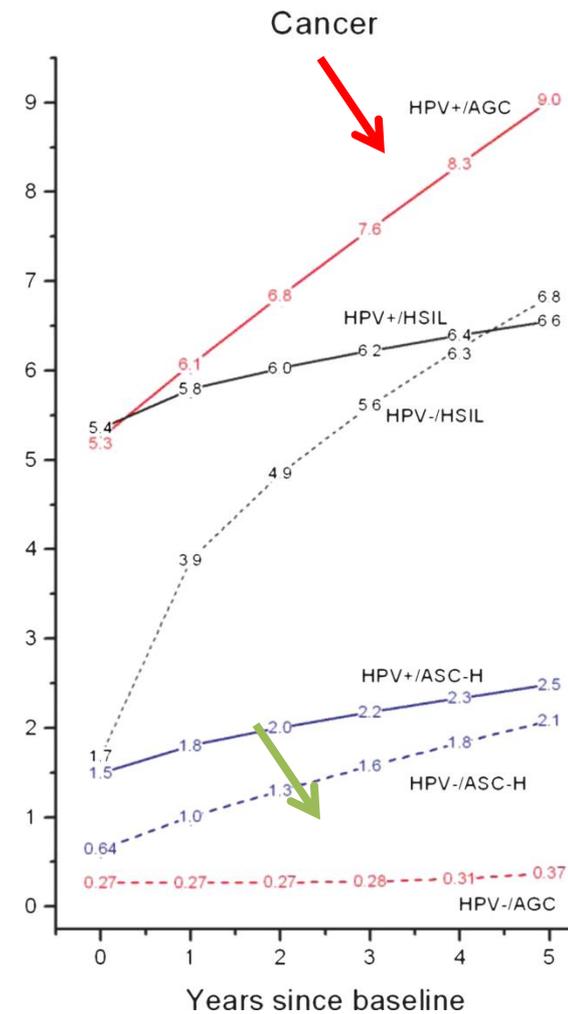
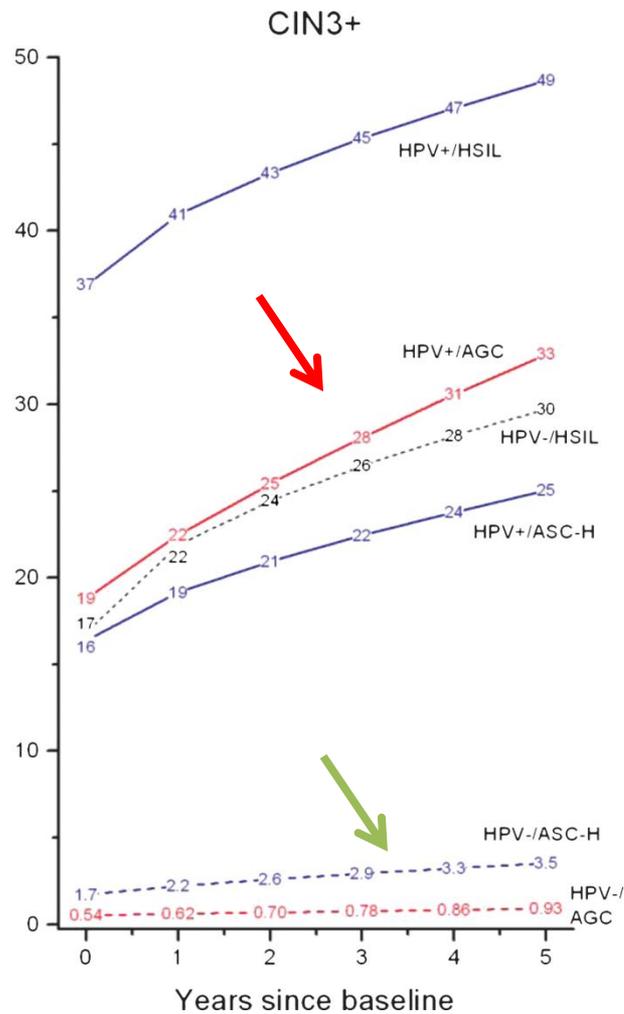
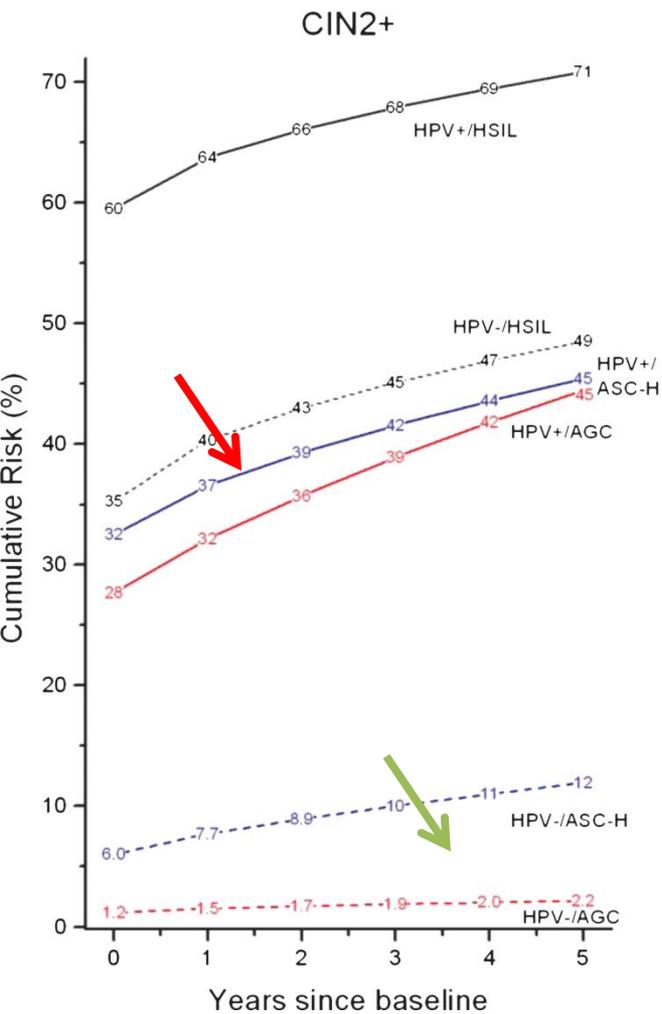
+ Not if patient is pregnant or ages 21-24

# Management of AGC

- AGC accounts for about 0.2% of Pap results
- Subdivided into
  - AGC not otherwise specified (NOS)
    - May be endometrial, endocervical, or “glandular”
  - AGC favor neoplasia
    - >30% have CIN2+
  - Adenocarcinoma in situ (cytologic AIS)
    - 50% have histologic AIS, >30% have cancer
  - Subdivisions not analyzed in KPNC dataset
- Most women with AGC have CIN, not AIS
  - Immediate CIN3+ risk = 6%, with cancer in 2%

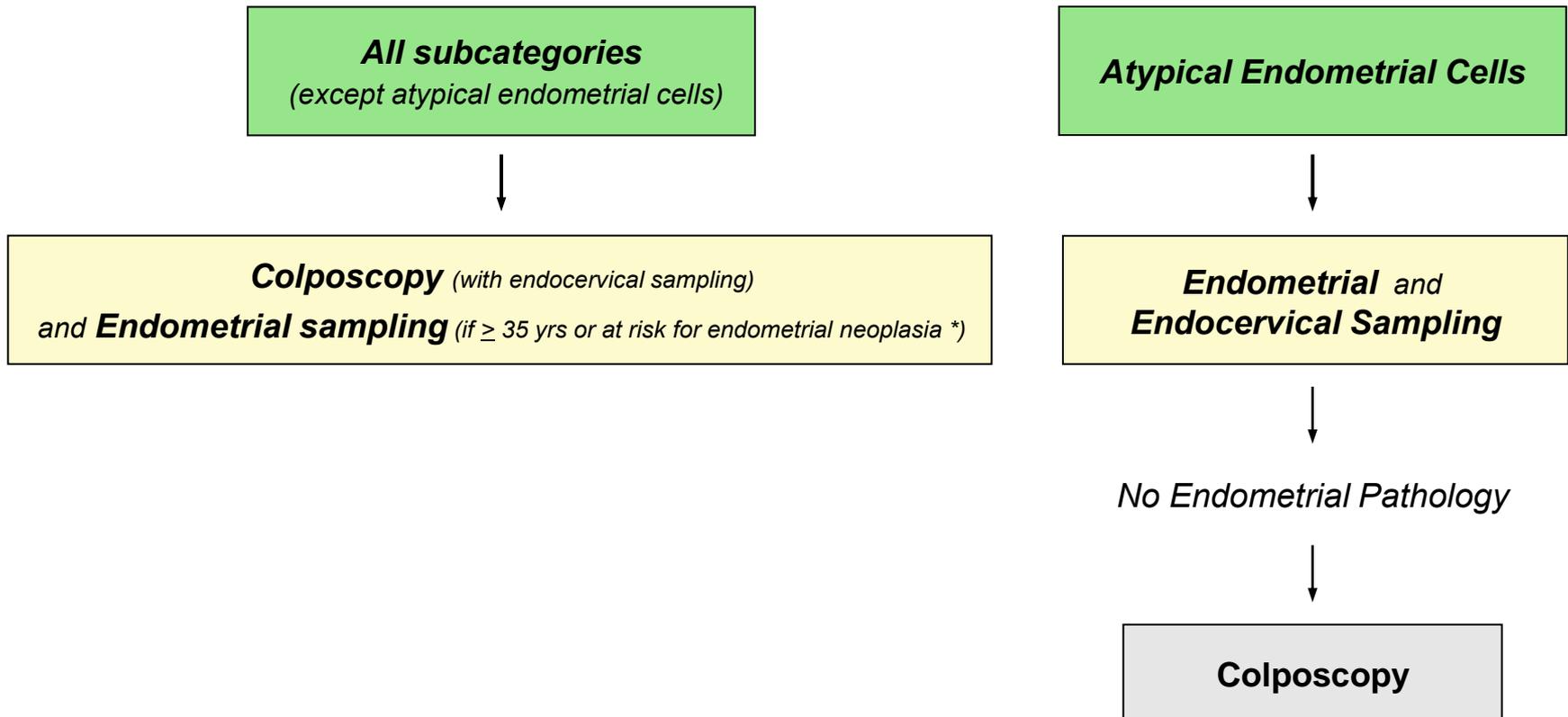
# Management of AGC in cotesting

- HPV results can direct evaluation
  - HPV- raises suspicion of endometrial disease
    - Esp in older/obese/oligomenorrheic women
    - Cervical lesions still must be excluded
  - HPV+ focuses suspicion on cervix/endocervix
    - Cancer risk at 5y is 9%, higher than HPV+ HSIL
- Since initial management isn't affected, cotesting is deferred till follow-up



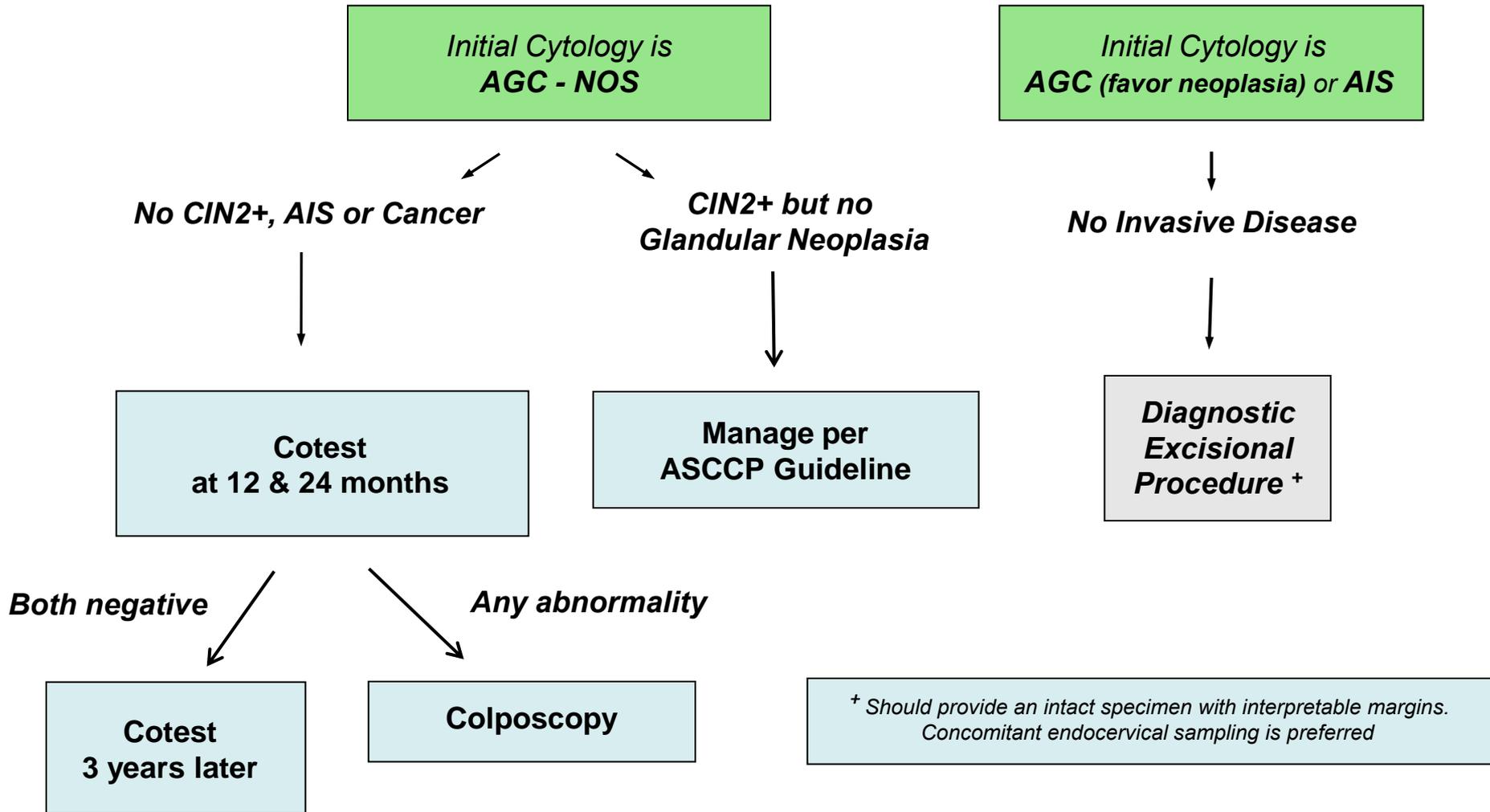
Risk of CIN is low if HPV negative, though endometrial lesions remain a concern.

## ***Initial Workup of Women with Atypical Glandular Cells (AGC)***



\* Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.

# Subsequent Management of Women with Atypical Glandular Cells (AGC)

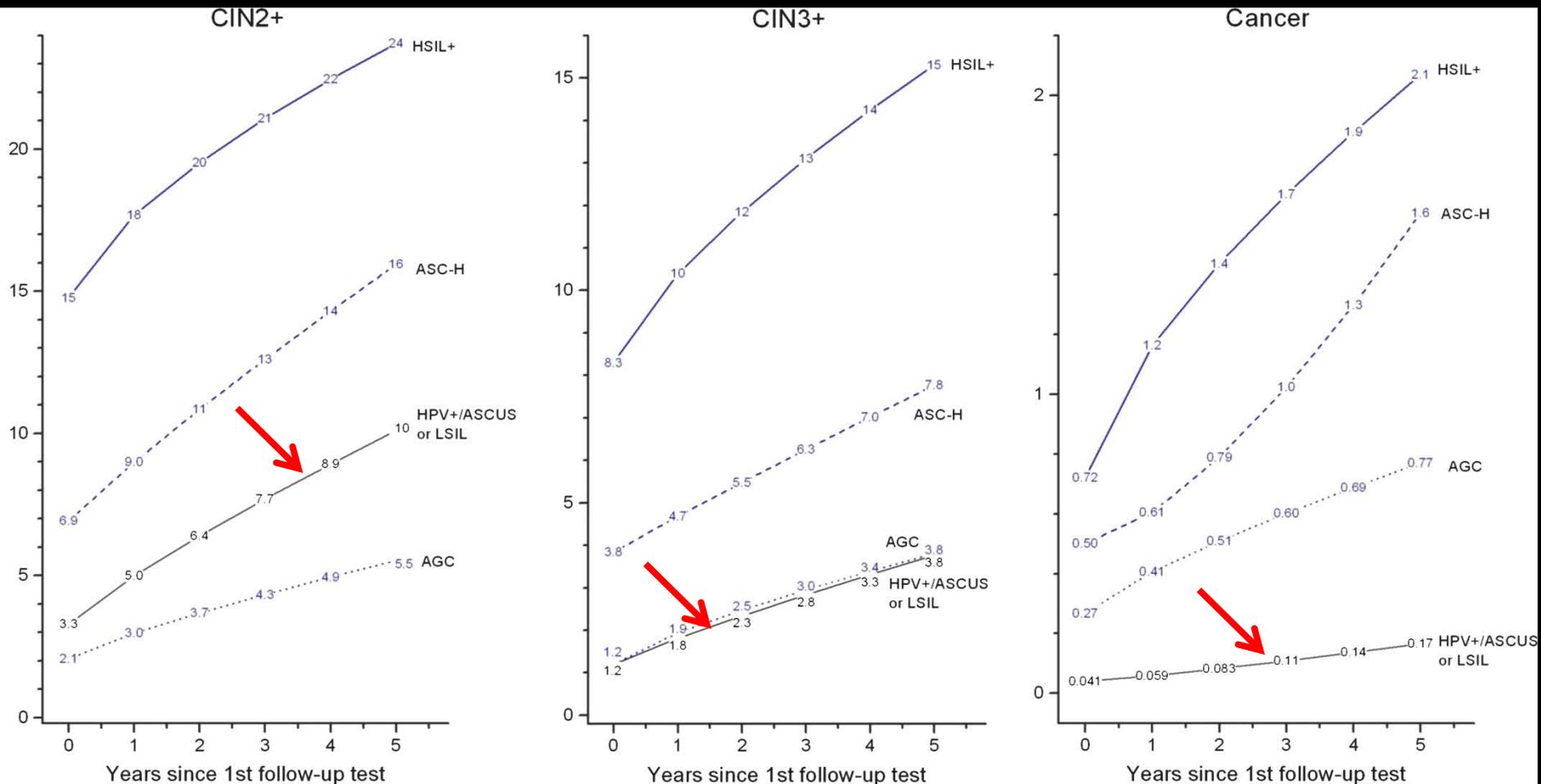


# <CIN2 after lesser abnormalities

- Lesser abnormalities include:
  - HPV 16/18+
  - Persistent HPV+
  - ASC-US → NOT ASC-H or AGC!
  - LSIL

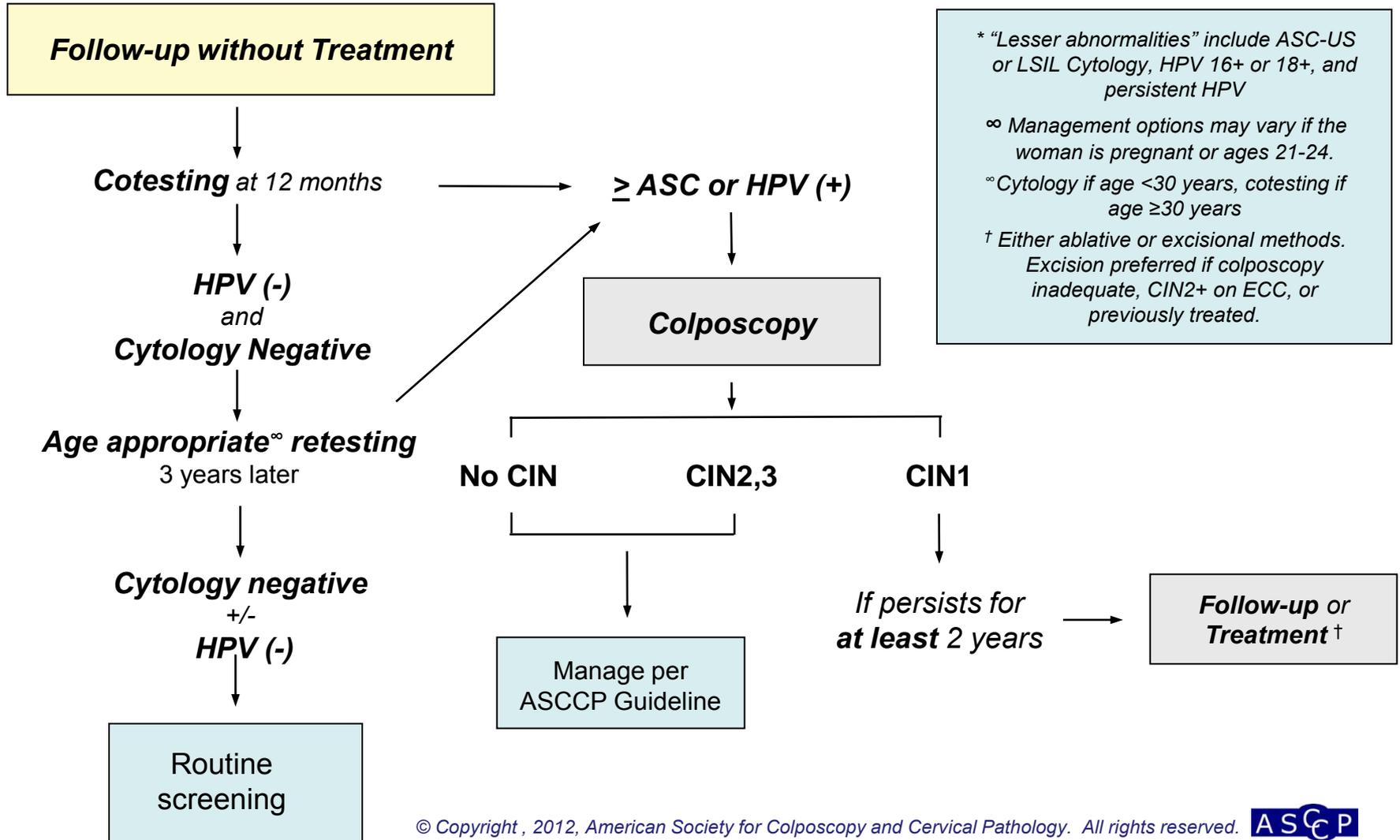
# <CIN2 after lesser abnormalities

- Risk for every cotest result is always higher after an initial abnormal result than after neg cotest result
  - Difficult to get to “routine screening” even if one cotest negative.
- 5y CIN3+ risk after 2 consecutive Pap-/HPV+ cotests is 7.4%--higher than after baseline LSIL
  - 5y CIN2+ risk is 16%
- Genotyping results not available in KPNC set



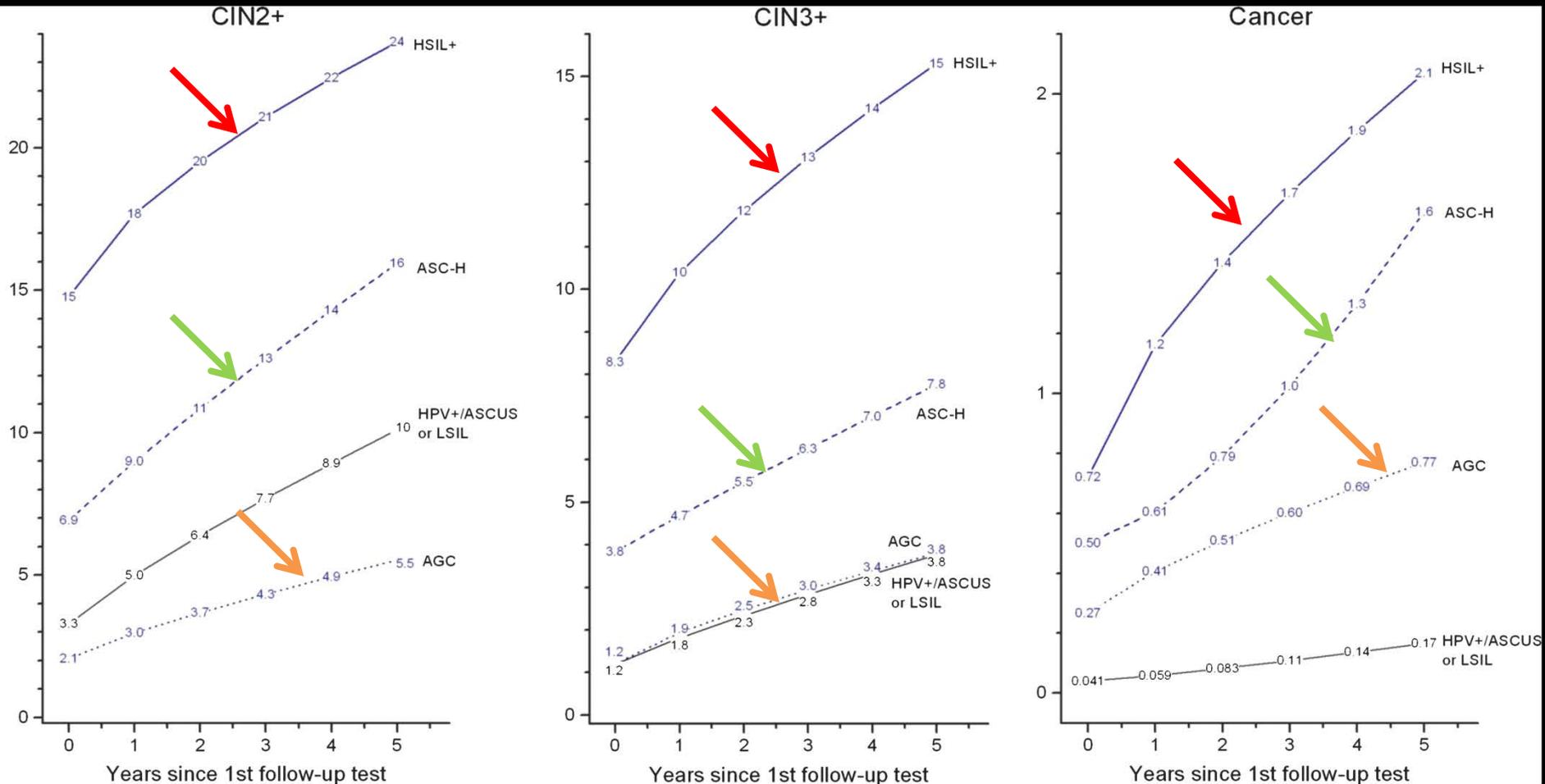
After neg/CIN1 at colposcopy/biopsy,  
 immediate precancer risk is low, but  
 surveillance is required.  
 Most CIN2+ by 5y are CIN2

# Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1) Preceded by "Lesser Abnormalities"\*<sup>∞</sup>



# <CIN2 after ASC-H/HSIL/AGC

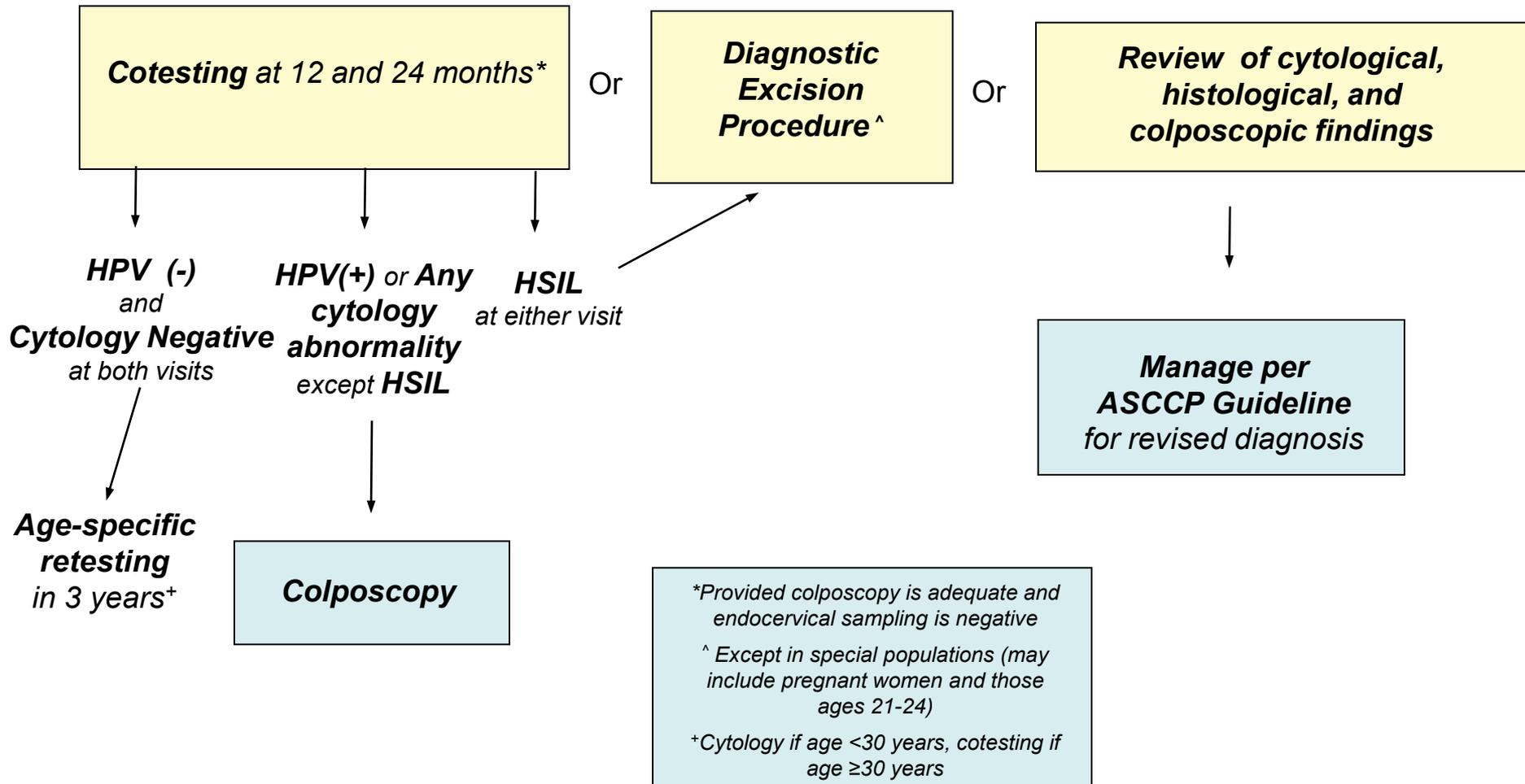
- 5y risk of disease remains high after these Pap results despite no high-grade lesion on colpo
  - Sensitivity of colposcopy is limited
  - Sensitivity improves with biopsy # up to 4
- Risk of CIN2+ after HSIL 24% at 5y despite neg/CIN1 on colpo/biopsy
- Risk of CIN2/CIN3 is low after AGC with neg/CIN1 at colpo is low, but cancer risk high



After neg/CIN1 at colposcopy/biopsy,  
risk rises rapidly.

AGC is of special concern for cancer risk

# Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1) Preceded by ASC-H, HSIL or AGC Cytology



## <CIN2 in women 21-24

- Near-zero cancer risk in this age group
  - Missed CIN unlikely to result in harm
  - Overtreatment may harm future pregnancies
- Potential for harm to future pregnancies means “more conservative (not similar) mgmt for similar risks” in women 30-64yo
- 5y CIN3+ risk after ASCUS/LSIL =3%
  - Risk must be lower after prevalent lesions found
- 5y CIN3+ risk among 21-24yo women with HSIL=28%, with ASC=16%

# Management of Women Ages 21-24 with No lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1)

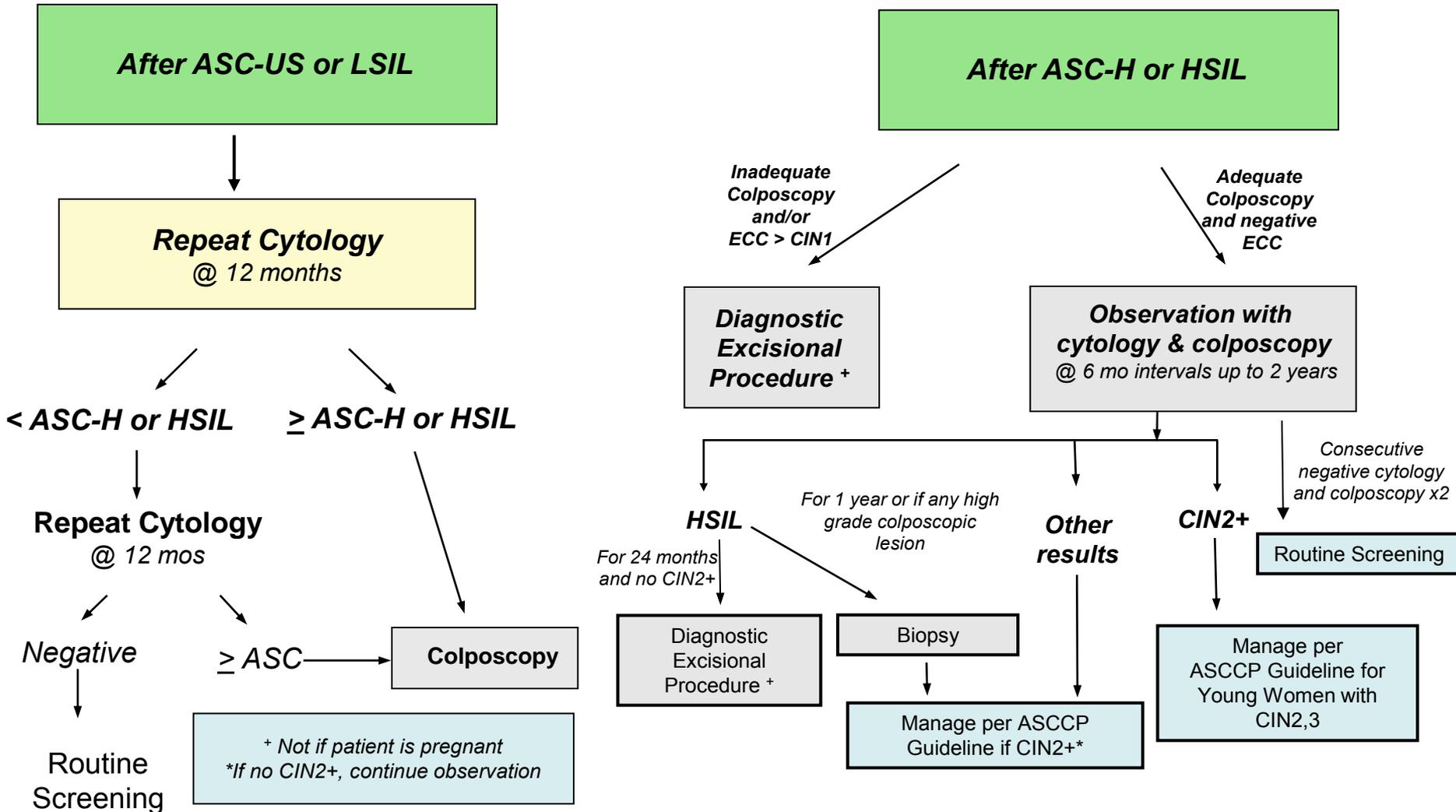


Fig. 15

# Management of CIN2, 3:

## Natural history

- Natural history of untreated CIN 2
  - 43% of CIN 2 lesions will regress
  - 35% will persist as CIN 2,
  - 22% will progress
- Natural history of untreated CIN 3
  - 32% of CIN 3 lesions will regress
  - 56% will persist
  - 14% will progress

Mitchell MF et al. J Natl Cancer Inst Monogr 1996;21:17-25.

ASCP

AMERICAN SOCIETY  
FOR COLPOSCOPY AND  
CERVICAL PATHOLOGY

*The society for lower genital  
tract disease since 1964*

# Management of CIN2,3

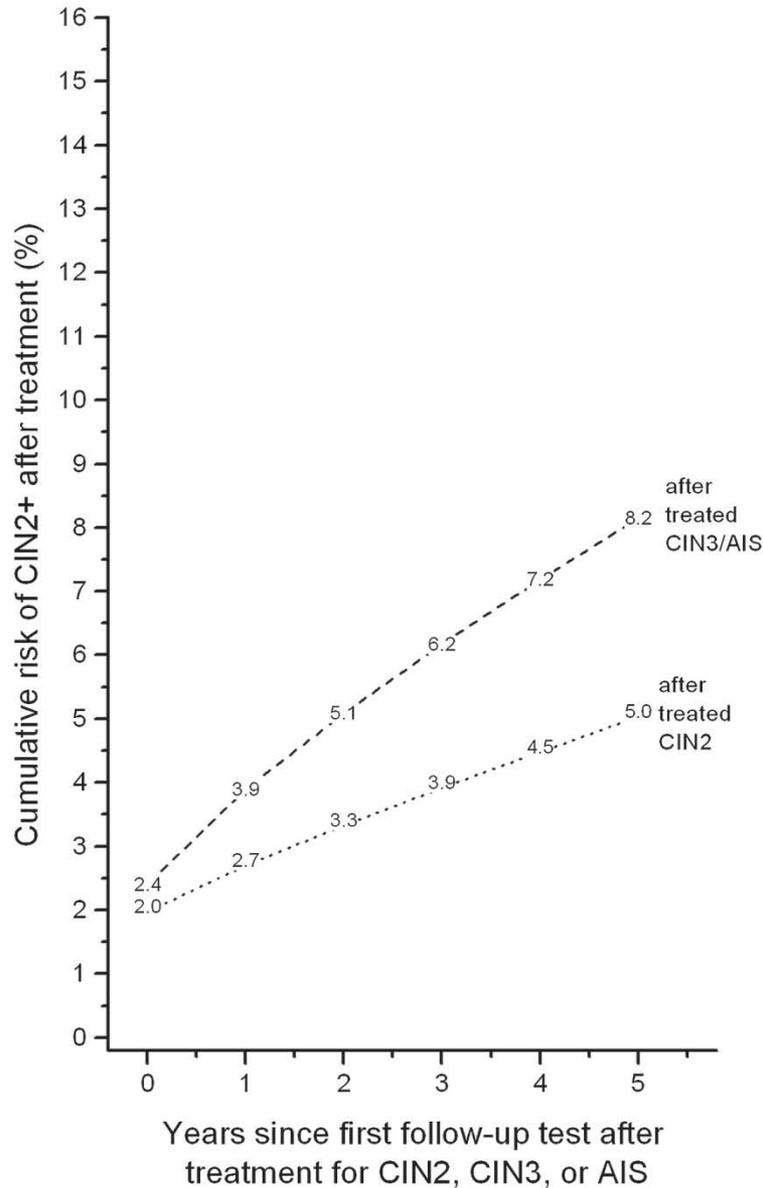
- RCTs show similar outcomes (about 10% failure risk) among women with CIN2,3 after ablation or excision
  - Excision will provide histologic specimen
  - LEEP has shorter operating time, less bleeding than knife conization, but more margin artifact
  - No ablation unless cancer excluded: -ECC, adequate colpo, no cancer by Pap or colpo
  - Excise if prior treatment (risk of skip lesions)

Mitchell MF et al. *Obstet Gynecol.* 1998;92:737-744.

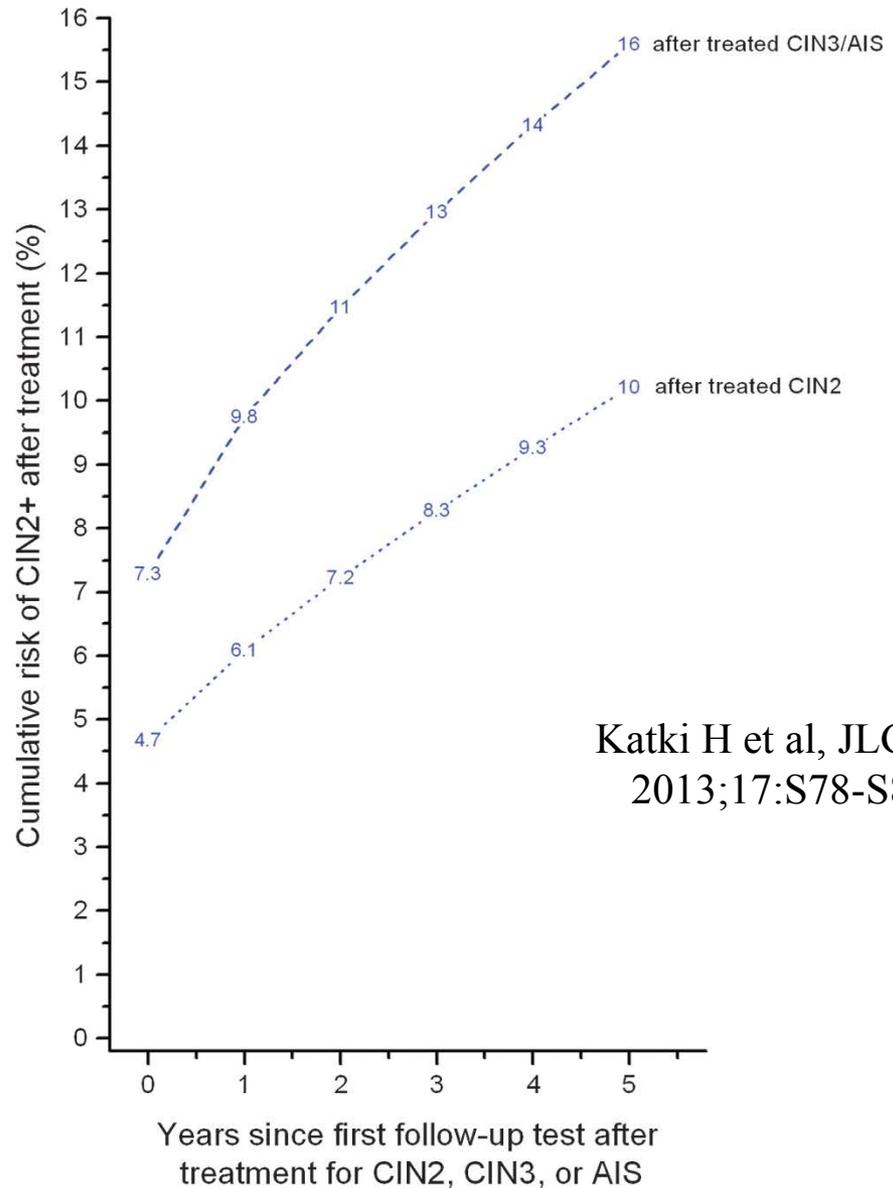
Persad VL, et al. *J Low Genit Tract Dis.* 2001;5:199-203.

Nuovo J, et al. *Int J Gynaecol Obstet.* 2000;68:25-33.

HPV+/ASC-US or LSIL antecedent



AGC, ASC-H, or HSIL+ antecedent



Katki H et al, JLGTD  
2013;17:S78-S84

Risk of recurrence after treatment of CIN2+ among women 25+

# Management of CIN 2, 3

## Rationale for follow-up after treatment

- Most recurrences present within 24m
  - Among 2240 women followed after treatment of CIN
  - 75% of recurrences occurred in the first 24 months
- Recurrences seen 20+ years after treatment

→ Intensive surveillance initially, but some surveillance long term

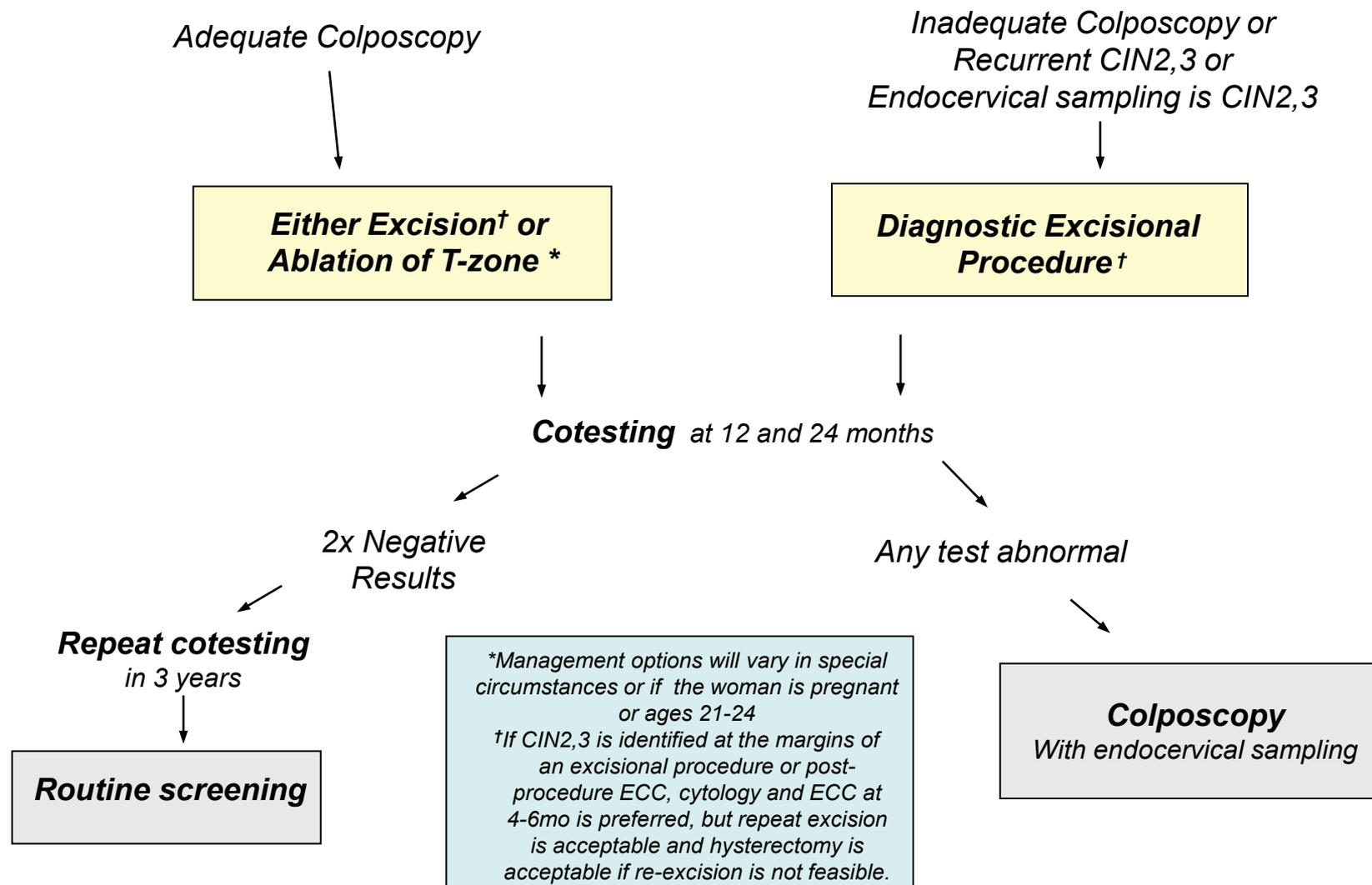
Persad VL et al. *Low Genit Tract Dis*, 2001;5:199-203  
Hellberg and Nilsson. *Gynecol Oncol* 1990;38:166-9  
Kalliala et al *BMJ* 2005;331:1183-5

# Post-treatment utility of HPV testing

## Treatment failure rates

	N (%) HPV-	N (%) HPV+
Paraskevaidis (2001)	3 (7%)	38 (93%)
Zielinski(2003)	1 (17%)	5 (83%)
Debarge (2003)	5 (19%)	22 (81%)
Alonso(2006)	1 (3%)	35 (97%)
Verguts (2006)	0	6 (100%)
Kreimer (2006)	3 (9%)	29 (91%)

# Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 and 3 (CIN2,3) \*



# Managing CIN2,3 in “young women”

- “Young women”: “Those who after counseling by their clinicians consider risk to future pregnancies from treating cervical abnormalities to outweigh risk for cancer during observation of those abnormalities. No specific age threshold is intended.” (NOT 21-24)

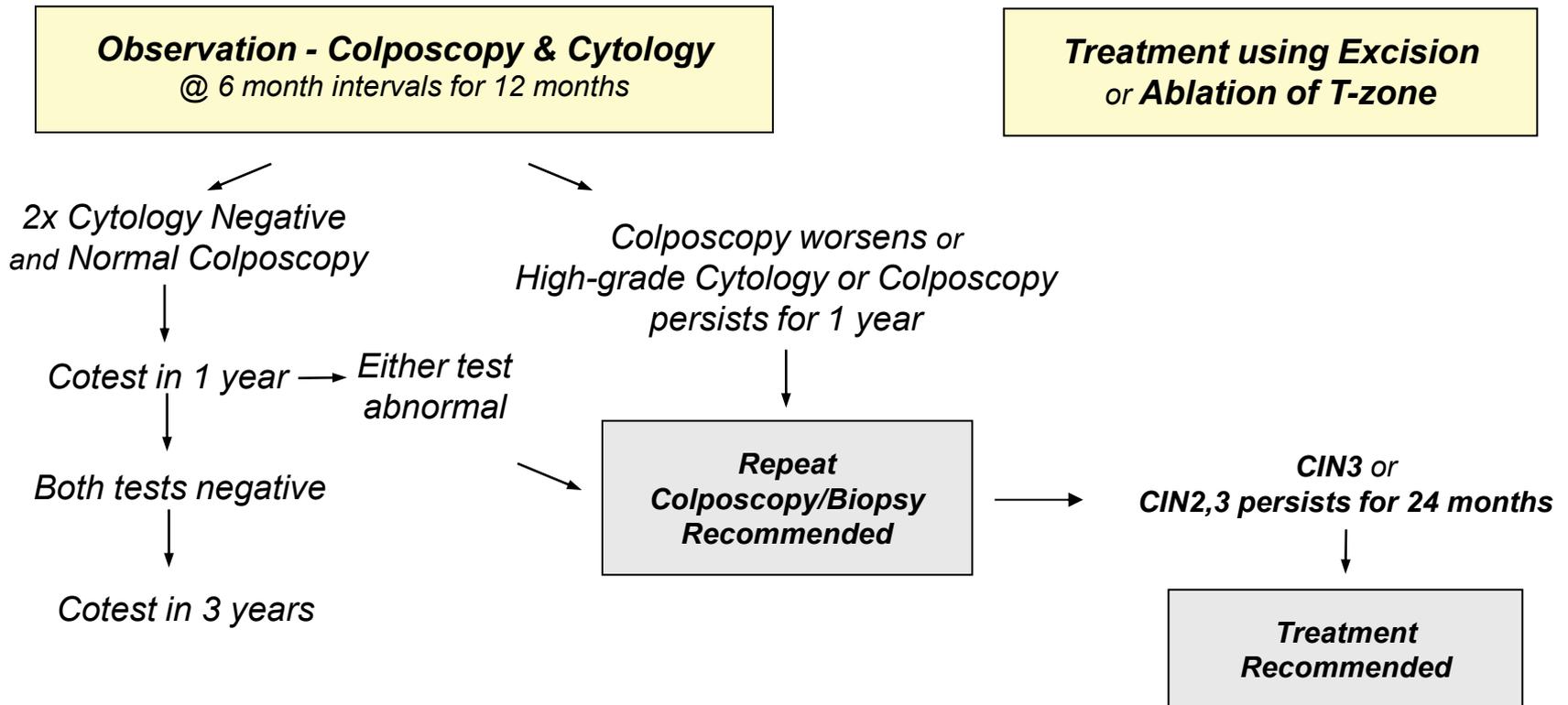
Massad LS et al. JLGTD 2013;17:S1-S27

- A 23yo who's been sterilized isn't young
- A 38yo in treatment for incompetent cervix may still be young

# Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2,3 (CIN2,3) in Special Circumstances

## Young Women with CIN2,3

*Either treatment or observation is acceptable, provided colposcopy is adequate. When CIN2 is specified, observation is preferred. When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.*



# Managing AIS at excision

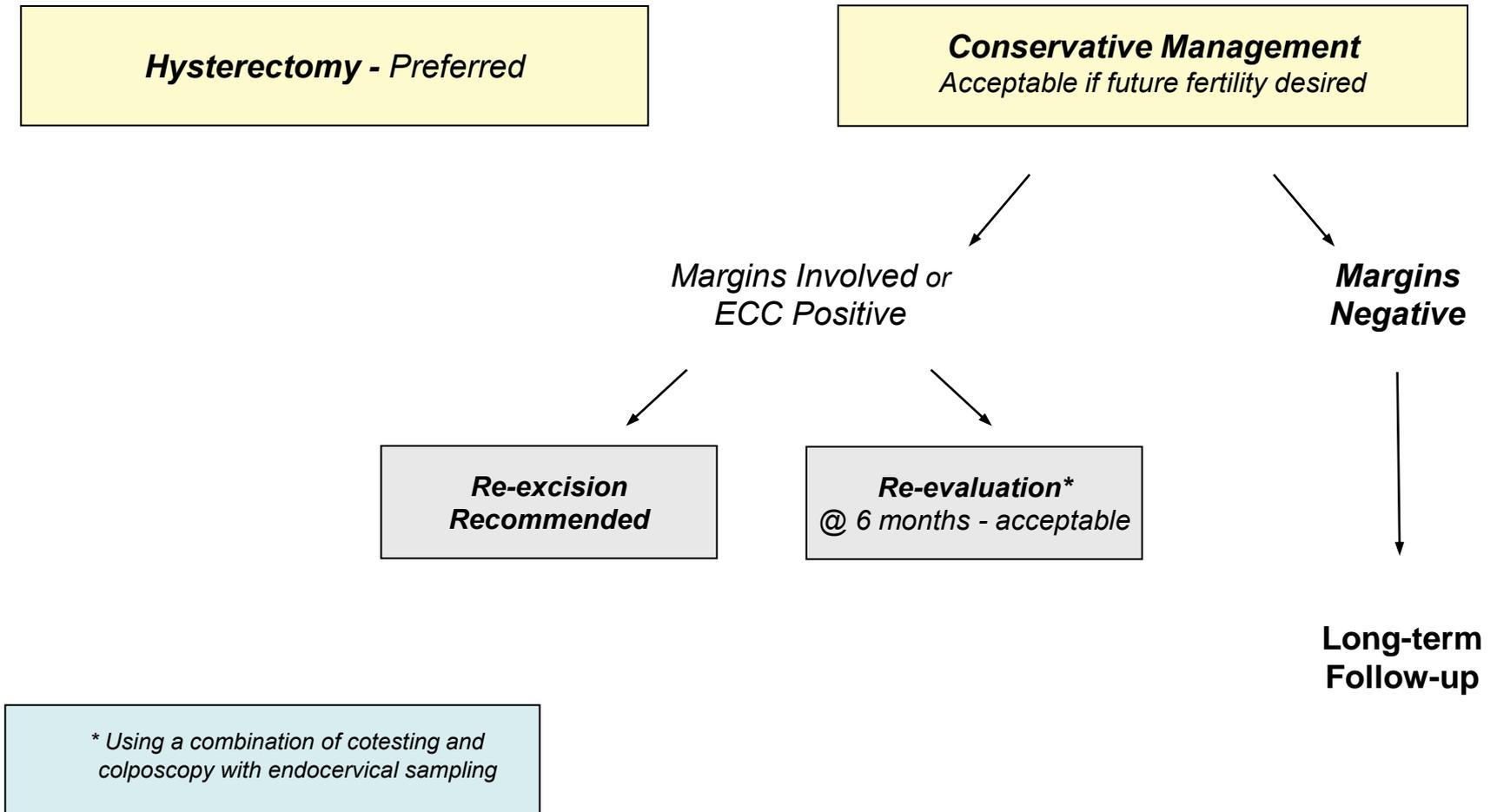
- Exclude cancer by cone
  - Knife or large loop aiming for intact specimen with interpretable, preferably clear margins
  - Not top hat LEEP
- May occur deeper within canal
- Difficult to see colposcopically
- Risk of persistent AIS after cone with clear margins=10%
- Neg HPV test a strong predictor of clearance

# Histologic AIS

## Margin status and persistence

- Among 1101 women after conization for AIS:
  - 55% with + margin but only 23% with –margin had persistence at hysterectomy
  - Only 7% recurred among 560 women managed conservatively
    - Only 1 had invasive cancer (0.2%)
  - Risk of +margin lower after CKC than LEEP

# Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure



# Managing biopsies reported as LSIL/HSIL

- Terminology developed under LAST
  - Eliminates CIN2
  - CIN3 is HSIL
  - P16<sup>ink4a+</sup> CIN2 is HSIL
  - P16<sup>ink4a-</sup> CIN2 is LSIL
  - P16<sup>ink4a+</sup> CIN1 is HSIL—test only if CIN2 suspected
  - P16<sup>ink4a-</sup>/not tested CIN1 is LSIL
- Little evidence base for determining long-term management
  - Guidance should be considered preliminary

# ***Interim Guidance for Managing Reports using the Lower Anogenital Squamous Terminology (LAST) Histopathology Diagnoses***

***Low Grade Squamous  
Intraepithelial Lesion  
(LSIL)\****



***Manage like  
CIN1***

***High Grade Squamous  
Intraepithelial Lesion  
(HSIL)\****



***Manage like  
CIN2,3***

*\*Histopathology Results only.*

# For more information

- Explanatory text available at J Lower Genit Tract Dis 2013;17:S1-S27
- Algorithms are available for free download (read only) at [www.asccp.org/consensus2012](http://www.asccp.org/consensus2012)

# 2012 Guidelines Steering Committee

